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# Neurodegenerative Diseases and Pivotal Therapies

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## ABSTRACT

Treatments for neurodegenerative diseases are moving away from only treating symptoms (such as levodopa for Parkinson's and cholinesterase inhibitors for Alzheimer's) and toward molecule-specific, disease-modifying medications. Immunotherapy to target protein aggregation (amyloid-beta, tau, α-synuclein), gene therapy, CRISPR-based genome editing, medication delivery by nanotechnology across the blood-brain barrier, and microglial cell replacement therapies are some of the major developments. Both active and passive immunization methods are being developed to lessen the build-up of harmful proteins that cause neurodegeneration. Gene therapy and RNA editing are methods used to target mutations with CRISPR or rectify genetic flaws (such as those in Huntington's disease), with RNA-based editing providing a reversible substitute for DNA alteration. For Alzheimer's disease the current treatment options available are NMDA receptor antagonists (memantine), cholinesterase inhibitors (donepezil, rivastigmine). For Parkinson's disease MAO-B inhibitors and dopamine precursors like levodopa are the conservative medicine. To manage functional decline, speech, occupational, and physical therapies are essential. Research focuses on employing early diagnostic tests (EMG, EKG, neuroimaging) to start treatment before extensive brain damage occurs, as well as combining medicines to target many disease pathways at once. Additionally, we examine the treatment techniques that are being developed now or in the future with the goal of normalizing these pathways, which may potentially strengthen the brain's ability to deal with harmful protein species. These innovative pharmacological strategies may be used in combination therapy intended to restore brain function. With an emphasis on cutting-edge immunotherapies like vaccine therapy, we hope to shed light on well-known immunotherapeutic approaches being developed to combat neuroinflammation-induced neurodegeneration.

## KEYWORDS

Neurodegenerative Disease, Therapies, Astrocytes, Microglia

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## INTRODUCTION

Neuroinflammation is the name for inflammation of nerve tissue that happens in response to a variety of stimuli, including autoimmune, traumatic brain damage, infection, and toxic metabolites. Because post-mitotic nervous system cells are unable to regenerate, neuroinflammation—a crucial mechanism for preserving healthy central nervous system (CNS) function following insults like physical trauma and infections—is tightly controlled. It also plays a significant role in a number of neurodegenerative [1] and psychiatric [2] illnesses. Reactive astrocytes and invading leukocytes aggravate inflammatory reactions in the central nervous system (CNS), which are triggered by microglia, the local innate immune cells [3]. Low-grade chronic neuroinflammation, which can cause collateral damage greater than the initial insult, is present in most neurodegenerative illnesses [4]. These disorders are thought to be caused by activated microglia, astrocytes, and other immune cells releasing cytotoxic substances over time, which can lead to neurodegeneration and persistent neuronal damage and brain atrophy in addition to altering the neurocircuitry [4]. Progressive degeneration of particularly sensitive neurons in distinct central nervous system (CNS) regions characterizes neurological disorders (NDs) [5,6]. The development and progression of NDs are influenced by a variety of factors, such as an excessive buildup of misfolded proteins, insufficient proteasomal complexes clearance, oxidative stress, low activity of endogenous antioxidant enzymes, mitochondrial dysfunction, low levels of neurotrophins, neuro-inflammation, and various genetic perturbations [7]. Depending on where they occur, neuronal loss, gliosis, or demyelination might impair thinking skills, produce behavioral problems, or affect motor function. Memory loss/dementia, AD, decreased mobility, motor dysfunction, and attention problems are the key characteristics of 4 NDs. PD, which stands for progressive weakening and cognitive function loss. Auto-immune-mediated neuronal degeneration, Amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) [8,6,9]. Due to their high disability-adjusted life years, a measure of the years of healthy life lost to sickness, NDs have a considerable negative impact on quality of life. According to epidemiological studies, the prevalence of these disorders, including AD and PD, is rising internationally along with life expectancy [10,11]. The primary cause of disability and mortality in elderly persons has been progressive neuronal loss, accompanying stroke, ischemia, and excruciating pain brought on by NDs [8,6,9]. The primary cause of disability and mortality in elderly persons has been progressive neuronal loss, accompanying stroke, ischemia, and excruciating pain brought on by NDs. Some traditional pharmaceuticals used to treat NDs have unavoidable negative effects [8]. Besides, most of these drugs are expensive. Therefore, there is a critical need for the creation of novel therapies and neuroprotective drugs with increased efficacy and fewer side effects in order to stop the progression of NDs.

A progressive loss of neurons in various parts of the central nervous system (CNS) is a hallmark of neurodegenerative illnesses, which are linked to cognitive, psychological, and motor impairments as a result of atrophy of the affected areas [12]. According to Mortada et al., neuropathology, neuroinflammation, immunotherapy, and neurodegenerative illnesses together account for a significant portion of the world's disease burden. In many developed nations, dementia is a public health concern. Because aging is a major risk factor for the most prevalent neurodegenerative disorders, the economic and social effect of these illnesses on healthcare systems will probably continue to rise dramatically in the

upcoming decades as people age and live longer [13]. According to projections, the global population of those over 60 would increase from 901 million in 2015 to 2.1 billion by 2050 [14]. Elderly people are predicted to spend the majority of their later years in poor health due to an increase in age-related illnesses that will coincide with longer life expectancies. Dementia, which affects 44 million people worldwide and is predicted to reach 135 million by 2050, is indeed a major source of disability in the elderly [15]. The two most prevalent neurodegenerative diseases, Parkinson's disease (PD) and Alzheimer's disease (AD), affect about 36 million individuals globally. The necessity to find new therapeutic targets to stop the course of disease is highlighted by the lack of effective disease-modifying medications and the failure of the majority of clinical trials for novel therapies. The multifactorial aetiology and varied disease history of the majority of progressive neurodegenerative illnesses present a significant barrier to the development of therapeutic methods [16-18]. The causes of the onset and course of the most prevalent neurodegenerative disorders, including AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), are not entirely understood.

Furthermore, patients differ greatly in the duration and severity of their diseases, making effective therapeutic measures more difficult to implement. Proteasomal dysfunction, oxidative stress, and neurotoxic protein misfolding are common pathogenic processes found in the majority of progressive neurodegenerative disorders [19]. There is mounting evidence that neurodegeneration and hazardous misfolded protein complexes are causally related. Although their clinical relevance is still up for debate, atypical protein aggregates are now thought to be a primary characteristic of the majority of neurodegenerative diseases, including PD, ALS, and HD [20].

**Microglia and Astrocytes: The key Players in Neurodegenerative diseases**

Neurodegenerative conditions like Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis are linked to neuroinflammation. In the central nervous system, microglia and astrocytes are important modulators of inflammatory reactions. Microglia and astrocyte activation can be classified as either neuroprotective (M2-phenotype microglia and A2-phenotype astrocytes) or neurotoxic (M1-phenotype microglia and A1-phenotype astrocytes). However, the different morphologies of microglia and astrocytes might not be reflected in this binary classification. The phenotypic distribution of these activated glial cells can alter as neurodegenerative illnesses progress, and their interaction is also quite complex. Developing effective treatments for neurodegenerative illnesses requires a deeper comprehension of the functions of astrocytes and microglia. A defense system called neuroinflammation first shields the brain from various diseases by eliminating or suppressing them [21]. By encouraging tissue healing and eliminating cellular debris, this inflammatory response may be advantageous. Sustained inflammatory responses, however, are detrimental, and they inhibit regeneration [22,23]. Endogenous (such as genetic mutation and protein aggregation) or environmental (such as infection, trauma, and medications) variables can cause inflammatory stimulation to persist [24,25]. Neurodegenerative illnesses may result from the ongoing inflammatory reactions that include astrocytes and microglia [22]. The central nervous system is made up of two types of cells: glial cells and neurons [26]. Glial cells were thought of being supporting cells for neurons because they do not generate electrical impulses. In terms of cellular diversity and function, glial cells have been shown to be superior than neurons [27]. Astrocytes, oligodendrocytes, and microglia are examples of glial cells that have the ability to control neuronal activity [26,28]. Astrocytes and microglia have a variety of roles in the brain, including innate immune responses. Both have historically been divided into two diametrically opposed phenotypes: neurotoxic and neuroprotective. Based on their

activation status, microglia are classified into two phenotypes: M1 (classical activation) and M2 (alternative activation) [24,29]. Astrocytes can release pro-inflammatory or immunoregulatory mediators based on the polarization state phenotypic, just like microglia [25]. Nonetheless, it is thought that astrocytes and microglia exhibit a variety of reactive phenotypes that are connected to the location, kind, and stage of neurodegenerative disorders [30-32]. Additionally, the phenotypic changes of microglia and astrocytes, their loss of neuroprotective roles, and their acquisition of neurotoxic functions are complex and may vary depending on the severity and stage of neurodegenerative illnesses. As a result, the different phenotypes of microglia and astrocytes cannot be represented by the straightforward dichotomized classification [30]. Because of these factors, the M1/M2 and A1/A2 designations were used sparingly in this text, only appearing in the references where they were utilized. Instead of being two different populations, they should be viewed as being on a spectrum. This intricacy may be the cause of anti-inflammatory medication trials' failure to demonstrate appreciable therapeutic benefits thus far. Here, we examine the functions of inflammatory reactions in neurodegenerative illnesses, including AD, PD, and ALS, with an emphasis on the functions of astrocytes and microglia and their interactions. Additionally, suggestions are offered to ensure the success of clinical trials. Furthermore, research on medications that can reduce neuroinflammation and biomarkers to gauge it are covered.

## Microglia

The primary innate immune cells and the first to react to pathological insults, microglia are widely dispersed throughout the brain [33,34]. Depending on the region, microglia make up 5–12% of the mouse brain's total cell population. They can exhibit a variety of morphologies, including compact spherical, longitudinally branching, and radially branched [35]. By taking part in three crucial processes, they contribute to host defense mechanisms and homeostasis [36]. The first role is to use their sensomes, which are encoded by different genes, to sense changes in their surroundings [37]. The second is the physiological housekeeping role, which involves myelin homeostasis maintenance, synaptic remodeling, and migration to injured areas [36,38]. The third is defense against harmful stimuli, such as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Microglia express cellular receptors that may identify PAMPs and DAMPs, including viral receptors, nuclear oligomerization domain-like receptors, and toll-like receptors (TLRs) [24,25]. In reaction to these stimuli, microglia release chemokines, such as the C-C motif chemokine ligand 2 (CCL2) and IL18, and proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-16, to attract more cells and eliminate pathogens [24,36]. Nevertheless, persistent neuroinflammation is linked to neurodegeneration and can cause neurotoxicity even if it is a neuroprotective mechanism [36]. Additionally, dystrophic morphology and an increased inflammatory response are displayed by microglia priming with aging and chronic stress [39]. Imaging and fluid biomarkers can be used to measure microglial activity. Because 11C-(R) PK11195 binds to the translocator protein, which is overexpressed in activated microglia, it can be utilized to measure microglial activation using positron emission tomography (PET) [40,41]. A fluid biomarker of microglial activation is the soluble triggering receptor expressed on myeloid cells 2 (sTREM2), a cleavage product of TREM2 produced on the cell surface of microglia [42,43]. According to recent research, the amount of sTREM2 in the cerebrospinal fluid (CSF) is associated with the level of sTREM2 in plasma, indicating that the CSF sTREM2 may be a biomarker for microglial activation [43,44]. Depending on how activated they are, microglia in the central nervous system (CNS) can either be neuroprotective or pro-inflammatory. Pro-inflammatory cytokines are detritus from infections or injured cells that cause pro-inflammatory factors such IL-1β, TNF-α, IL-6, nitric oxide (NO), and proteases to be expressed by resting microglia. These factors have a negative impact on neurodegenerative illnesses [24,31]. On the other hand, neuroprotective microglia are activated by IL-4, IL-10, IL-13, and transforming growth factor-β (TGF-β). This results in the release of various factors such as FIZZ1, Chitinase-3-Like-3 (Chi3l3), Arginase 1, Ym1, CD206, insulin-like growth factor 1 (IGF-1), and Frizzled class receptor 1 (Fzd1) [24,31,45,46]. These microglia-derived components may be linked to tissue repair and neuroprotection. For

instance, pro-inflammatory cytokines including IL-6, TNF-α, and NO are known to be suppressed by IL-4 [47,48]. Aging-related remyelination may be impacted by alternating between these two phenotypes [25,49]. Microglia's shift from a neuroprotective to a neurotoxic phenotype is known to be influenced by obesity, insulin resistance, and type 2 diabetes [46,50.51]. Fasudil (Rho kinase inhibitor), Jumonji domain containing 3 (Jmjd3, H3K27me3 demethylase), minocycline, Copaxone (glatiramer acetate), dimethyl fumarate (Tecfidera), cromolyn, CHF 5074, fingolimod, masitinib, glycogen synthase kinase-3 inhibitor, histone deacetylase inhibitor, peroxisome proliferator-activated receptor, and JAK/STAT inhibitors [52-57]. Depending on the stage of neurodegenerative disorders, each phenotype's proportion may vary [46]. Depending on the time range, treatments that target the phenotypic balance may have varying impacts [46]. Therefore, regulating the course of neurodegenerative illnesses may require balancing and alternating between the phenotypes of microglia at particular times and in particular people. Since it is difficult to follow patients for longer periods of time in clinical trials, the drugs that modulate microglial activation are more likely to show protective effects in clinical trials that:

1) Use participants with more pro-inflammatory than neuroprotective microglial phenotypes;

2) Enroll participants who are likely to show progression within a few years; and

3) Have confirmed the pathology of the disease, such as amyloidopathy or tauopathy; without a pathological insult, the glial cells may not change.

Additionally, microglia actively participate in intricate neurodevelopmental programs such synaptic pruning and neurogenesis [49]. Microglia provide trophic support, synaptic regulation, and neuronal reconfiguration in the adult brain by interacting with neurons and macroglia cells [50,51]. A number of dynamic microglial processes, including as altered cell shape (ramified or quiescent/resting, active or ameboid), surface phenotype, and proliferative responses, are brought on by loss of homeostasis or tissue alterations that occur in AD [52]. Because of their varied phenotypes and activation routes, microglia play a complex role in the course of AD [42]. The pattern recognition receptors (PRRs), which include scavenger receptors, Toll-like receptors (TLRs), and receptors for advanced glycation end (RAGE), are a family of innate immune cell receptors expressed by microglia. The neuroinflammation seen in AD may be caused by accumulating Aβ, as many Aβ species, particularly neurotoxic oligomeric Aβ, can activate microglia by binding to PRRs [53,54]. Microglia activation has been linked to neuroprotective effects in the early stages of illness by phagocytosing dead cells, cleaning cell debris, releasing neurotrophic factors, and eliminating the detrimental stimuli indicated by hyper-production of Aβ [55]. However, these cells are exposed to a state of chronic activation and inflammatory cytokine release due to the harmful stimuli's persistence across the disease continuum, which causes neurotoxicity and neurodegeneration. These mechanisms produce danger-associated molecular patterns (DAMPs), which further activate microglia and start a self-sustaining proinflammatory cascade that results in the ability to remove Aβ [47,56]. Furthermore, microglia appear to play a significant role in the spread of tau pathology. Nevertheless, it is still unknown if microglia cause tau pathology by releasing substances that worsen it or by failing to engulf it [52]. Therefore, determining how illness-specific microglial phenotypes contribute to the development of AD may be useful in developing immunotherapies that, depending on the stage of the disease, either increase or reduce inflammation.

Microglia research has grown exponentially over the last 20 years. Our comprehensive understanding of microglia has greatly benefited from technological advancements. The development of our understanding of microglia identity will be demonstrated here as an illustration. The microglia were separated into "resting microglia" and "activated microglia" in the middle of the 1970s. At the time, it was widely accepted that under physiological conditions or in the normal brain, microglia exhibit a ramified phenotype and remain static. Under pathological conditions or in the diseased brain, these "resting microglia" change into

"activated" microglia, which have an ameboid morphological appearance. However, in 2005, researchers discovered that microglia are incredibly dynamic and continuously survey the parenchyma with their highly motile processes, even in the absence of pathological challenge, thanks to the development of a two-photon in vivo imaging system and the creation of a heterozygous Cx3cl1GFP/+ mouse line. Recent research has found several microglial states in both healthy and sick brains using single-cell mass cytometry and single-cell sequencing. Microglia are no longer thought to merely go from "resting" to "activated" in reaction to damage, illness, or other difficulties. Rather, in the setting of health or illness, microglia are constantly active, change states, and carry out various tasks in reaction to their surroundings [58,59]. The following are some of the most important discoveries throughout the past few decades:

(1) Microglia are diverse and dynamic;

(2) They interact with other brain cell types;

(3) They have both beneficial and detrimental effects in neurodegenerative diseases;

(4) They can be reprogrammed;

(5) Peripheral immunity controls microglial response, such as through the gut–microbiota–brain axis; and

(6) Microglia also age.17.

A comprehensive evaluation of all the advancements in microglial research in health and disease is outside the purview of this page and has been done elsewhere [60-66]. With the rapid advancement of methods like single-cell omics, live imaging, and instruments for manipulating microglia both in vivo and ex vivo. Microglial replacement therapy has proven to be a helpful treatment for several illnesses. For example, bone marrow-derived cells with a microglial phenotype are implanted in the brain parenchyma when wildtype bone marrow is transplanted into mecp2-deficient animals, stopping the course of the disease [67]. According to another comprehensive study, hematopoietic stem cells are crucial following Mr. BMT transplantation, and total bone marrow is heterogeneous and ill-defined [68]. Immature monocytic cells generated from bone marrow have the ability to adopt a microglia-like phenotype and share a number of characteristics and functions with native microglia [69]. Mr. BMT makes up for the impaired capabilities of senescent resident microglia in AD since resident microglia seem to deteriorate in AD [70]. ALS is a deadly neurological illness that worsens over time. Microglia's functional characteristics were changed and the neural cell microenvironment was enhanced by BMT of mSOD1-transgenic mice with BMCs [71]. Additionally, the symptoms of CNS disorders can be lessened by transplanting genetically altered BM cells. Additionally, Mr. BMT techniques are always being refined. A recent study created a method for quickly and almost entirely replacing microglia in mice with circulation-derived myeloid cells, which reduces neurodegeneration and improves motor dysfunction in prosaposin-mutant mice and eliminates the significant variability that follows conventional BMT [68]. Research has been done on the technique of removing microglia in particular areas [72]. Microglial recolonization in a brain region of interest will undoubtedly have higher application possibilities, even though the use of Mr. MT in disorders is somewhat uncommon. We hypothesize that lentiviral vectors can be used to transduce therapeutic genes into stem or progenitor cells, resulting in the stable integration of genes like TREM2 in AD animals or MeCP2 in Rett syndrome. It is possible that we can cure more difficult genetic disorders and prevent immune rejection at the same time by genetically altering the retrieved normal microglia. Migratory cells that react to brain traumas are known as CCR2-positive cells [73]. Consequently, the mechanism of microglial replacement in the brain may be connected to the function of CCR2. Furthermore, a study found that engrafted BM-derived myeloid cells exhibit markedly elevated levels of CD68, a lysosomal marker linked to an elevated activation or phagocytic state [74]; microglial engraftment influences neuronal communication and astrocyte activation [74]. Therefore, molecules like CX3CR1/CX3CL1 and CD200/CD200R [75] that influence microglial activation or interactions with other cells may also influence microglial replacement. The effectiveness of replacing external microglia is directly

impacted by the rate at which resident microglia are removed. According to our latest study, astrocytes in the brain mainly eliminate microglial debris via opsonizing C4b [76]. Astrocyte reactivation is probably impacted by microglia engraftment. Clinical therapy development might benefit from more investigation into the processes of microglial replacement.

Numerous reputable pharmaceutical firms have started creating medications that specifically target microglia. TREM2 is the target of three medications used to treat Alzheimer's disease: Alector's AL002 (NCT05744401), Denali's DNL919 (NCT05450549), and Vigil Neuroscience's VGL101 (NCT05677659). AL002 is a TREM2 agonistic antibody that stimulates microglia by activating TREM2 and inducing their value addition. This promotes Aβ phagocytosis and delays the onset and progression of Alzheimer's disease. MS4A4A is the therapeutic target of Alcobra's MG01CI (AL014), which is also utilized to treat Alzheimer's disease (NCT02126995). Roche's gantenerumab can attach to aggregated Aβ proteins and break down amyloid plaques by attracting activated macrophages and microglia. An FDA-approved treatment for Alzheimer's disease is gantenerumab. Clinical phase II trials for medications like VGL101, AL002, and Canakinumab (ACZ885) (NCT04795466) are advancing more quickly. However, medications like DNL919 (NCT05450549), ABBV-0805 (NCT04127695), and AL003 (NCT03822208) are presently in clinical phase one. DNL201, the first small molecule LRRK2 inhibitor, began clinical trials in 2017 (NCT03710707) and showed in a Phase I trial that it inhibited LRRK2 kinase activity in healthy individuals. In both fundamental research and clinical Phase I, Matthew et al. comprehensively assessed the cascade of DNL201 in treating Parkinson's disease (PD) in 2022 and discovered that a safe dose might address lysosomal dysfunction in PD patients [77]. Nevertheless, it seems improbable that DNL201 might repair damaged or dead dopamine-producing neurons and so alleviate Parkinson's disease symptoms. Additionally, Denali researchers assessed the DNL151 small molecule drug's effectiveness. They discovered that DNL151 also suppresses LRRK2 and has a longer half-life in the blood than DNL201, which may lessen how frequently patients need to take the medication. Consequently, DNL201 clinical trials were discontinued at this point. Phase III clinical studies for DNL151 were finished in August 2023 (NCT05418673). AbbVie launched two Phase II clinical research programs in February 2017 to assess the potential of ABBV-8E12, an investigational anti-tau monoclonal antibody medication, for the treatment of progressive supranuclear palsy (PSP) (NCT02985879) and early AD (NCT02880956). The pathogenesis of these two neurodegenerative illnesses is marked by elevated Tau levels in the brain. But in Phase II of PSP in 2019, ABBV-8E12 was a complete failure. In a similar vein, Biogen declared that Gosuranemab, its anti-Tau antibody, did not fulfill its primary endpoint in TANGO, a Phase II clinical research in AD, and that Gosuranemab did not offer any therapeutic effect above placebo. The clinical development of gosuranemab was then stopped. There are now five major groups of medications that target microglia to treat neurodegenerative disorders. The first group reduces the production of pro-inflammatory factors, chemokines, and cytotoxic chemicals by inhibiting activated microglia with immunosuppressive or anti-inflammatory medications. This method is still useful even though it was put forth before scientists had a complete understanding of the immunological system of the brain. The second class of medications is based on the pro-inflammatory and anti-inflammatory phenotypes that activated microglia exhibit. The illness can be treated or lessened by using medications to change their pro-inflammatory to anti-inflammatory characteristics. Targeting microglia phenotypic alteration to treat disease may be beneficial, even though the dichotomous classification of microglia is no longer advised. Additionally, this type of treatment is currently being tested in clinical trials. The phagocytosis of microglia rather than their phenotype is the main target of the third class of medications. It is hoped that medications will be able to regulate their phagocytosis and quickly eliminate undesirable tissue or debris from the illness. With the quick development of single-cell sequencing, the fourth class of medications was proposed to provide therapeutic methods by focusing on particular disease-related microglia subtypes. In an effort to prevent and treat disease using neonatal microglia rather than active ones, the fifth class of medications focuses on the depletion and regeneration of microglia. Although several are in clinical trials, there are presently no medications that target microglia to treat

CNS problems in a variety of people. Sadly, several of these medications have been terminated as a result of poor development or the identification of superior substitutes. The fundamental reason for these occurrences is that there are still unanswered questions about medication development research or that theories pertaining to microglia need to be supported by adequate data. Drug discovery and therapy targeting microglia have a lot of potential because microglia are important in neurodegenerative disorders. However, numerous pertinent research findings that will be acquired by researchers in the future are still required to substantiate this. Future studies could concentrate on the areas in which microglia contribute to illness and provide targeted medications. Additionally, researchers could employ histology techniques to concentrate on novel microglia classifications or functions, focusing on certain functions to either exploit or prevent them.

## Astrocytes

The most prevalent type of glial cells in the brain are astrocytes [78]. Recent research has shown that astrocytes have active and crucial roles in brain homeostasis, despite the fact that they were previously thought to have solely passive activities [79]. They govern blood flow, preserve the blood-brain barrier (BBB), supply neurons with energy metabolites, alter synaptic activity, manage neurotrophin production, eliminate dead cells, and regulate the extracellular balance of ions, fluid, and transmitters as well as scar formation [78-80]. Glial fibrillary acidic protein (GFAP), S100B, YKL040, and D-serine are currently evaluated as CSF biomarkers, while GFAP and S100B are evaluated as blood biomarkers [81]. For biomarker imaging, magnetic resonance spectroscopy. Astrocyte reactivity is evaluated by 11C-deuterium-L deprenyl (11C-DED) PET and 11C-BU PET [81,43]. The degree of reactive astrogliosis, a defining feature of CNS disease, can be determined by changes in astrocyte shape and molecular expression as evaluated by GFAP [80]. Astrocyte defects during the early stages of injury, such as spinal cord injury (SCI) and experimental autoimmune encephalomyelitis (EAE), are consistently linked to worsened clinical outcomes, neuroinflammation, BBB alteration, and neuronal death [78]. Conversely, a study in a chronic experimental EAE mouse model revealed that astrocytes produce lactosylceramide (LacCer), which promotes inflammation and neurodegeneration [82]. These findings suggest that astrogliosis can have either positive or negative effects, depending on the disease, the time period, and other microenvironmental cues like microglia. Astrocytes can exhibit a continuous spectrum of various response profiles at the same time. Thus, more research should be done on the heterogeneity of reactive astrocytes [31]. Astrocytes have immunoregulatory (neuroprotective) and pro-inflammatory subpopulations, just like microglia. Pro-inflammatory reactive astrocytes generate proinflammatory molecules including IL-1β, TNF-α, and NO, which are known to have detrimental effects, and upregulate a number of genes, including complement cascade genes [24,31]. By contrast, numerous neurotrophic factors and thrombospondins are upregulated by neuroprotective reactive astrocytes [31]. Astrocytes may be neuroprotectively activated by anti-inflammatory cytokines like IL-4, IL-13, and IL-10. These alternatively activated astrocytes may then release TGF-β, IL-4, and IL-10 [66]. Pro-inflammatory microglia can release inflammatory mediators such IL-1α, IL-1β, TNF-α, and C1q, which can activate pro-inflammatory astrocytes and trigger a secondary inflammatory response [83,84]. Numerous additional cytokines, sphingolipids (sphingosine 1-phosphate and LacCer), and neurotrophins can trigger harmful astrocytic signaling pathways [78]. During neuroinflammation, astrocytes increase the transmembrane receptors for tropomyosin receptor kinase B (TrkB) and IL-17. When IL-17 binds to its receptors, pro-inflammatory cytokines are produced and nuclear factor κB (NFκB) activator 1 (Act1) is recruited [85]. While stimulation of TrkB by the agonist brain-derived neurotrophic factor (BDNF) exerts negative effects on neurons, conditional animals lacking TrkB can be shielded against EAE-induced neurodegeneration [86]. Astrocytes that react to specific pathways, on the other hand, are protective because blocking the mediators of these protective pathways exacerbates neuroinflammation and neuronal cell death. The glycoprotein gp130 mediates the first protective route, which reduces neuroinflammation and is connected to SHP2/Ras/ERK activation [87]. The CNS damage caused by Toxoplasma encephalitis and EAE in mice is exacerbated by the absence of gp130, a

signal transducer for the IL-6 cytokine family [87,88]. TGFβ, which has significant immunosuppressive qualities, mediates the second protective mechanism. Following a stroke or Toxoplasma infection, astrocytic TGFβ signaling may mediate the suppression of NFκB signaling and lessen neuroinflammation [89,90]. Interferon (IFN)-γ signaling mediates the third protective pathway. Even though IFN-γ is a pro-inflammatory cytokine, inhibiting its signaling in astrocytes exacerbates leukocyte infiltration and mortality in the late stages of EAE in mice [91]. Lastly, in a number of neurological illness models, the estrogen receptor (ER) alpha signaling pathway in astrocytes has shown anti-inflammatory and neuroprotective benefits [92]. Astrocytes express the transcription factor signal transducer and activator of transcription 3 (STAT3), which is phosphorylated upon damage. After SCI in mice, ablation of STAT3 in astrocytes exacerbates inflammatory cell infiltration, neuronal loss, and demyelination [93]. Activated astrocytes can increase STAT3 activity by secreting BDNF [94]. In a different in vitro and in vivo investigation using a SCI mouse model, STAT3 knock-out reduced astrogliosis and interfered with scar formation, which were linked to increased lesion volume and exacerbated inflammation [95]. Thus, STAT3 is linked to a neuroprotective impact and appears to play a crucial role in reactive astrogliosis. Reactive astrocytes' neuroprotective properties may be mediated by the JAK-STAT3 pathway. It is unknown, therefore, what chemical mechanism underlies the generation of neuroprotective reactive astrocytes [96]. Furthermore, polarization may exist in states other than neuroprotective or proinflammatory [97]. Thus, more research should be done on the molecular underpinnings and heterogeneity of reactive astrocytes. They control cerebral blood flow, facilitate synaptic development and transmission, and take part in neurovascular coupling and the preservation of the blood–brain barrier (BBB) [98]. Astrocytes, which make up the parenchymal portion of the blood-brain barrier, control the formation of endothelial cell-to-cell junctions that maintain the BBB's structural and functional integrity by secreting soluble factors like growth factors (such as glial cell-line neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoetin-1 (ANG-1), morphogens (Sonic hedgehog (Shh) and Wnt), and extracellular vesicles [99,100]. In many neurological conditions linked to BBB disruptions, astrocyte–endotheliocyte communication is essential. Perivascular astrocytic end-feet are not securely sealed under physiological conditions [99]. Conversely, in neuroinflammatory conditions associated with AD, which are marked by BBB disruption and leukocyte infiltration into the central nervous system, end-feet of reactive astrocytes establish a parenchymal line of defense by triggering the formation of tight junctions in response to inflammatory cues, thereby tightening the border to restrict peripheral immunocyte infiltration into the brain [101]. Depending on the time and illness context, astrocyte activity in this situation may either worsen inflammatory responses and tissue damage or encourage immunosuppression and tissue healing [102]. Additionally, astrocytes play a neuroprotective role in AD by reducing plaque accumulation through Aβ clearance [103]. On the other hand, unpleasant stimuli, Aβ, or active microglia induce astrocytes. Certain astrocyte-activating signals, such as interlukin-1 alpha (IL-1α), complement component 1q (C1q), and TNF-α, are released by activated microglia. These signals then activate β-secretase and γ-secretase activity, cleaving APP and stimulating astrocyte β-amyloid formation, thereby augmenting neuronal β-amyloid production [104]. Thus, inflammatory activation of astrocytes can lead to increased expression of APP, β-secretase, and β-site APP-cleaving enzyme (BACE1), suggesting a feed-forward mechanism of astrocytic Aβ synthesis [105,106]. Every acute damage and long-term neurological condition is accompanied by reactive astrocytes, such as reactive microglia. Since it is now evident that reactive astrocytes exist in at least two distinct states of activation, A1 and A2, it is crucial to ascertain whether they are present in both human disease and mouse models, as well as what specific roles they play in the pathophysiology of disease. While the benefits of scar-forming reactive astrocytes that encapsulate damage or seal a compromised blood-brain barrier are easily understood, other types of astrocyte reactivity seem to be detrimental. Although reactive astrocytes give regenerated axons trophic support [107], they can potentially prevent axon regeneration [108]. Additionally, several genes that induce synapse development are upregulated by reactive astrocytes. These genes include those that encode thrombospondins, which may aid in brain healing [109-111]. However, these alterations may also produce undesired synapses that cause neuropathic pain or epilepsy [112]. A factor that can

destroy motor neurons is released by astrocytes cultured from the Sod1G93A mutant mice [113-115]. In a similar vein, alpha motor neurons deteriorate in ALS patients due to a cytotoxic substance generated by A1 reactive astrocytes. It's interesting to note that other motor neuron subtypes that are spared from the disease are not harmed by this factor [111]. A1 reactive astrocytes are found in brain regions implicated in neurodegeneration in a number of human disorders, such as Alzheimer's disease, multiple sclerosis, ALS, Parkinson's disease, and Huntington's disease. Given that A1s release a neurotoxin that kills neurons and oligodendrocytes and numerous classical complement cascade components that can exacerbate synaptic degeneration [116-118], this highlights the potential significance of reactive astrocytes in chronic neurodegenerative disease. The presence of A1s in human neurodegenerative disease implies that neuroinflammation may be aiding or perhaps causing neurodegeneration, despite the long-held belief that neuroinflammation is subsequent to neurodegeneration. Finding this toxin's identify will be crucial in order to develop novel treatments that either prevent its creation or counteract its effects. In addition to being closely linked to neuroinflammation and neuroinflammatory reactivity in astrocytes and microglia, the NFkB pathway regulates cytokine production and cell survival [119-121]. Additionally, it is extensively active in neurodegenerative diseases [122,123]. The NFkB pathway is activated by a variety of pro-inflammatory substances, including cytokines, bacterial or viral antigens, amyloid, stress, free radicals, and many more [120,123]. The relationship between activation and astrocyte reactivity has been unclear thus far due to the widespread activation of the NFkB pathway in illness; it has not yet been determined if astrocyte reactivity is necessary. Given that selective inhibition of NFkB signaling in astrocytes only momentarily changed Gfap expression levels at the onset of motor dysfunction in a murine model of ALS, the Sod1G93Amutation, it is plausible that the requirement for NFkB pathway activation is only temporarily important to astrocyte reactivity [124]. GFAP is one of the least increased reactive transcripts following damage, albeit it is unclear to what degree these cells were truly reactive [110]. A thorough examination of astrocyte gene changes in this paradigm could produce quite different findings. Similar to this, NFkB-GFP reporter mice bred with Sod1G93A ALS animals exhibit stronger activation in microglia cells than in astrocytes; however, astrocyte reactivity was only measured using GFAP immunoreactivity. In this paradigm, toxicity tests in cocultured cells revealed motor-neuron cell death, which was linked to substances released by microglia. However, since it appears that traditionally activated neuroinflammatory microglia have strong NFkB pathway activation, which is necessary for the activation of neuroinflammatory reactive astrocytes, it is unclear what percentage (if any) of contaminating astrocytes may be present in these culture systems [111]. Similarly, research on NFkB activation of astrocytes in mouse models of Huntington's disease [121] and rodent models of Alzheimer's disease [125,126] suggests that NFkB activation in astrocytes may be crucial for the development of these diseases and chronic inflammation. Human ALS patients' spinal cords have NFkB pathway activation in astrocytes [122]. NFkB-activated astrocytes may therefore be detrimental astrocytes that contribute to neurodegeneration in a range of illness types in mice. When combined, these findings indicate that A1 reactive astrocytes are likely prevalent in numerous mice illness models because they also show NFkB activation [126]. On the other hand, a combination of recent research indicates that the activation of A2 (ischemic) scar-forming reactive astrocytes is likely mediated by the JAK-STAT3 pathway. Numerous cell processes, such as growth, proliferation, and differentiation, as well as some inflammatory processes, are regulated by this route [127]. During the early stages of brain development, the JAK-STAT3 pathway in astrocytes plays a crucial role in regulating the initiation of astrogliogenesis and the subsequent maturation of astrocytes [128,129]. JAK-STAT3 has been linked to scar-forming astrocyte reactivity following acute damage in a number of studies [130,127,107]. Additionally, "reactivity" in fly astrocyte-like cells is mediated by STAT92E, the Drosophila ortholog of STAT3 [131]. Inhibition of inflammatory signaling pathways can be the focus of clinical therapies. For instance, the acentral driver of A1 astrocyte activation, the NF-κB/STAT3 pathway, releases pro-inflammatory cytokines when STAT3 phosphorylation is inhibited [118,119] and discovered that miR-21a-5p inhibits the CNTF/STAT3/Nkrf pathway, which increases A1 polarization and causes inflammation. Research revealed that Cntfr α knockdown totally reverses the inhibitory impact of CNTF on A1s, but loss-of-

function of miR-21a-5p greatly increases this effect. The miR-21a-5p inhibitor greatly decreased the percentage of A1s in an animal model of traumatic spinal cord injury (TSCI) and enhanced neuron regeneration via increasing CNTF/STAT3 signaling axis activity. This neuroprotective effect was abolished in astrocyte-specific STAT3-deficient animals. Notably, miR-21a-5p alone may have a small impact on the A1/A2 marker balance even in the absence of exogenous CNTF treatment via controlling the basal expression level of Cntfr α, indicating a ligand-independent basal regulatory function [119]. Therefore, it is still unrealized to treat neurodegenerative illnesses by focusing on the miR-21a-5p/CNTF axis. Chi et al. discovered that via activating astrocyte TLR2 receptors and initiating the NF-κB signaling pathway, α-synuclein (α-syn) greatly increased complement C3 production (inhibition of TLR2/NF-κB resulted in a large drop in fluorescence intensity). When astrocyte-derived C3 binds to C3aR, it intensifies α-syn PFF-induced neuronal death [120]. Therefore, based on the mechanisms mentioned above, therapeutic strategies could be to stop C3-C3aR signaling, such as by using a C3aR antagonist (SB290157), which attenuates tau hyperphosphorylation through the GSK3β signaling pathway and inhibits neuronal apoptosis, or to block C3 production at the source, such as by applying a TLR2-specific antagonist (e.g., C29) or an NF-κB inhibitor (JSH-23). GSK3β inhibitors, such as TDZD-8, can also lessen initial neuronal apoptosis caused by complement C3 protein and α-syn PFF. Future research is also planned to use anti-C3 monoclonal antibodies to lower α-syn pathological burden and limit neuronal apoptosis, or to precisely shut down the astrocyte TLR2 gene using gene editing techniques. NF-E2-related factor 2 (Nrf2) in AD controls neuroinflammation via C3-STAT3 signaling and prevents A1-type astrocyte production by inhibiting NF-κB subunit p65 recruitment [121,122]. Different regulatory systems are involved in PD pathology: While NR1H4 provides neuroprotection by inhibiting the CEBPβ/NF-κB pathway, RGS5 exacerbates neurodegenerative disease by boosting TNFR signaling [123,124]. SerpinA3N increased KA-induced neuroinflammation in epilepsy models by triggering NF-κB activation and being associated with RYR2 phosphorylation. Ethanol activated NLRP6 inflammatory vesicles through miR-339 downregulation, while lipocalin-2 (LCN2) caused NLRP3 inflammatory vesicle-dependent astrocyte death via the 24p3R receptor in ischemic stroke pathology [125-127]. Through RhoGTPase, IL-10 and Cdc42 control astrocyte-microglia interactions in methamphetamine-induced neuroinflammation [128]. While ablation of Nurr1 promotes neuroinflammation by reducing GDNF, boosting proinflammatory factor release, and affecting BBB integrity, the LR agonist PEDF-34 suppresses astrocyte A1 polarization via the JNK/STAT1 pathway and reduces neuroinflammation in subarachnoid hemorrhage [129,130]. Through complex, disease-specific molecular networks, these studies collectively establish astrocytes as key orchestrators of neuroinflammation and cell death, thereby identifying crucial intervention nodes for the development of precision therapeutic strategies targeting astrocytic dysfunction. A crucial area for comprehending the pathophysiology of brain diseases is the developing paradigm of astrocytic metabolic reprogramming and inflammatory control. By preventing oxygen glucose deprivation (OGD)-induced TNF-α expression through NDRG2 protein stability, lactate acts as a neuroprotective metabolite in brain ischemia models, resulting in strong anti-inflammatory effects that lessen ischemic injury [131]. Similarly, 4-octyl itaconic acid ester (4OI) coordinates astrocytic neuroprotection in neonatal hypoxic-ischemic encephalopathy (HIE) via triggering the Nrf2 pathway to cooperatively regulate oxidative stress and inflammatory reactions [132]. The olfactory entorhinal cortex, hippocampus, and temporoparietal areas show a specific metabolic dissociation between increased 11C-acetate uptake and decreased 18F-FDG metabolism, according to advanced metabolic imaging of AD patients. Significantly, 18F-labeled progressive hypometabolism and 11C-labeled astrocytic functional loss in carriers of disease-causing mutations coincide, creating a useful biomarker for dynamic tracking of AD progression [133]. Through increased lactate synthesis and restoration of PC activity, sodium pyruvate, ethylpyruvate, and glucose show varying efficiency in restoring neuron-glial metabolic coupling after controlled cortical injury in TBI models [134]. On the other hand, a major metabolic pathway underpinning alcohol-related brain injury is shown by chronic intermittent ethanol exposure, which causes permanent impairment of cerebral lactate transport through MCT overexpression [135]. From a therapeutic standpoint, ginsenoside Rb1 exhibits remarkable neuroprotective efficacy by reducing astrocyte activation and

mitochondrial dysfunction following ischemic stroke by suppressing reverse electron transfer-mediated ROS generation and specifically inhibiting NADH dehydrogenase activity in mitochondrial Complex I [136]. When taken as a whole, these studies shed light on the complex multifaceted mechanisms by which astrocytes coordinate neuropathological processes via the metabolic-inflammatory axis, providing a strong basis for the development of precise neuroprotective strategies based on metabolic intervention. By rectifying disease-causing mutations in astrocytes or correcting aberrant gene expression, gene therapy offers a method for addressing the underlying causes of neurodegenerative disorders. The regulation of important metabolic pathways, the repair of genes that cause disease, and the creation of precision delivery systems are the main areas of current research, which is based on technological advancements in viral vectors, gene editing, and synthetic biology. Mutants PSEN1 and PSEN2 speed up the synthesis of Aβ1-42 in early-onset AD by changing the APP cleavage site. Additionally, the PSEN2 N141I mutation in patient-induced pluripotent stem cells (iPSCs) can be corrected using CRISPR-Cas9, returning the Aβ42/40 ratio to normal levels and rectifying the electrophysiological deficits in neurons [137]. CRISPR technology prevented the APP gene's interaction with β-secretase (BACE1) by targeting its C-terminal structural domain, which greatly decreased the production of Aβ [138]. The most popular and traditional way to distribute CRISPR/Cas9 is by viral vectors, however off-target alterations may cause serious side effects. Although they are frequently utilized for delivery, adeno-associated viruses (AAV) have a little packaging capacity (less than 4.8 kb) and can cause an immune response [139]. For instance, György et al. loaded the sgRNA and Cas9-coding sequences targeting the APPSW mutant allele into AAV vectors independently using a dualAAV vector partitioning technique. In order to inject dual AAV vectors, the in vitro model separated primary neurons from APPSW transgenic Tg2576 mouse embryos. The in vivo validation process involved injecting dual AAV vectors locally into the hippocampal region of adult Tg2576 mice. CRISPR/Cas9 can selectively damage APP and hence lower pathogenic Aβ, according to the results of both in vitro and in vivo trials [140]. Nonviral nanocarrier technology, which offers cheaper cost, improved specificity, more sample load, and lesser immunotoxicity, has also advanced quickly [141]. A Cas9-sgRNA ribonucleoprotein, which targets BACE1 specifically, was employed by Park et al. to construct a complex with a R7L10 peptide nanocomplex. According to the findings, the compound inhibited Aβ-related pathologies and cognitive impairments in two mice models of AD by reducing BACE1 expression and had no significant off-target mutations in vivo [142]. Non-viral vectors still face difficulties such poor penetration and vector material-related toxicity, even if they have lower off-target danger and delivery efficiency than viral vectors. Future advancements in the translation of clinical disorders will require the combination of gene editing and epigenetic modification technologies. Innovative approaches to neurodegenerative illnesses and brain injury repair have been established by recent advances in astrocyte-targeted gene therapy. NeuroD1 AAV gene therapy successfully corrects neuronal functional deficiencies in ischemic brain injury by using in vivo cellular reprogramming technology to transform glial cells into functioning new neurons [143]. In addition to dramatically improving cognitive abilities like short-term memory and spatial working memory for dopaminergic neurodegeneration in Parkinson's disease (PD), IGF-1 gene therapy also upregulates the expression of tyrosine hydroxylase in the caudate-crustal nucleus (CPu) and modifies the function of the nigrostriatal pathway [144]. AAV-mediated co-expression of NeuroD1 and Dlx2 transcription factors reprogrammed striatal astrocytes into GABAergic neurons, significantly extending the lifespan of the R6/2 model mice and improving motor function [145]. On the other hand, AAV2/5 vector-driven SREBP2 overexpression significantly extended the lifespan of the mice by activating the cholesterol biosynthesis pathway [146]. Through the activation of the cholesterol biosynthesis pathway, the restoration of synaptic transmission function, the reversal of the aberrant expression of dopaminereceptor D2 (Drd2), and the removal of the mutant Huntington's protein aggregates, expression improved the pathological phenotype of HD in multiple dimensions. Targeting and correcting astrocyte dysfunction is a crucial part of treating vanishing white matter disease (VWM), which is characterized by white matter loss. The AAV9-gfaABC (1)D-EIF2B5 vector achieved astrocyte-specific gene delivery through the GFAP promoter [147]. Through precise regulation of cholesterol metabolism,

synaptic plasticity, and protein homeostasis pathways, these studies not only show the special plasticity of astrocytes as prime targets for gene therapy, but they also establish a comprehensive multi-level therapeutic framework spanning cellular transformation to molecular repair, thereby laying solid theoretical and practical foundations for clinical translation. Astrocytes are appealing therapeutic targets for neurological illnesses given the significant scientific discoveries achieved in the last ten years. Drug delivery across the blood-brain barrier is a problem for treatment strategies that target astrocytes and other CNS-resident cells. It appears that this significant issue can now be appropriately handled thanks to recent advancements in medicine delivery. For instance, intraspinally injected poly (lactic-co-glycolic acid) nanoparticles are absorbed by astrocytes and remain for extended periods of time in the SCI rat model [148]. Several investigations have reported synthesized nanoparticles that can be employed for astrocyte-specific targeting [149]. Furthermore, polyamidoamine dendrimers given systemically colocalize with astrocytes engaged in the early stages of ischemic injury [150]. Other non-invasive molecular delivery methods that avoid the blood-brain barrier have also been developed, such as exosomes, neurotropic viruses, receptor-mediated transcytosis, and nanoparticles [151]. Astrocyte reactivity is modulated by metabolic pathways in a variety of neurological disorders, making them potential targets for therapeutic intervention [152-154]. For instance, miglustat, an FDA-approved glucosylceramide synthase (GCS) inhibitor used to treat Niemann-Pick disease type C [155] and type 1 Gaucher disease, reduces chronic progressive EAE in the NOD model by stopping immunometabolic pathways in pathogenic astrocytes [153]. Miglustat's therapeutic benefits include the inhibition of cPLA2–MAVS signaling in astrocytes, which increases CNS inflammation and obstructs the synthesis of lactate necessary for neuronal metabolic support. These results also point to additional GCS inhibitors as viable options for modifying astrocyte responses that encourage neurodegeneration and CNS inflammation. For instance, venglustat, a novel oral GCS inhibitor that penetrates the central nervous system and is being studied for the treatment of lysosomal storage diseases, may be a helpful tool to control astrocyte responses [156]. Targeting mitochondrial dysfunction, which has been connected to neurodegenerative illnesses like MS, AD, PD, and HD [157,158], is another metabolism-based strategy to modify astrocyte responses. For instance, in HD, low brain glucose levels cause striatal astrocytes to undergo metabolic reprogramming, which increases the generation of ROS and neuronal damage. A mitochondria-targeted antioxidant called XJB-5-131 reduces ROS-induced neuronal damage caused by astrocytes [152,154], demonstrating the possibility of treating neurological disorders by focusing on astrocyte metabolism. In both brain physiology and disease, cell-cell interactions are crucial. For example, interactions between astrocytes and microglia regulate neurodegeneration, CNS inflammation, and synaptic pruning [159-162]. Novel therapeutic targets can be systematically found by identifying the chemicals and processes controlling CNS cell–cell interactions using recently discovered techniques [159,163-165]. For example, we discovered novel roles for axon guidance molecules (EPHB3–ephrinB3, plexinB1/2–semaphorin4D) in astrocyte–microglia contacts that enhance CNS disease in EAE and possibly MS using RABID-seq, a technique that combines barcoded viral tracing with scRNA-seq. In this regard, a CNS-penetrant inhibitor of EPHB3 signaling reduced EAE pathogenesis in acute and chronic progressive models and inhibited the harmful activities of human and mouse astrocytes in vitro15. According to earlier studies on the role of EPH signaling in the pathophysiology of neurodegenerative diseases like AD280 and PD281, ephrinB3–EPHB3 signaling is a promising therapeutic candidate for modifying astrocyte and microglial pathogenic functions in MS and possibly other neurological disorders.

## CONCLUSION

With an emphasis on microglia and astrocytes, we examined the functions of neuroinflammation in neurodegenerative illnesses. Clinical or experimental research on therapies linked to neuroinflammation in neurodegenerative illnesses was also covered. The development of neurodegenerative illnesses may depend on the equilibrium between pro-inflammatory and neuroprotective glial cells. The stages of neurodegenerative diseases (more pro-inflammatory than neuroprotective) and patient conditions (confirmed

pathology of disease and likely to progress within a few years) may be critical for proving the benefits of anti-inflammatory treatments in clinical trials due to the complexity of microglia and astrocyte phenotypes and the variety of drug types. It is necessary to determine the roles of astrocytes and microglia at particular phases of particular diseases in particular patients. The next stage of the trials is to establish a consistent procedure for assessing each microglia and astrocyte phenotype in order to standardize subsequent assessment. Furthermore, it has been noted that reactive astrocytes and activated microglia interact. Novel astrocyte roles in health and disease have been identified thanks to recent technological advancements, underscoring their promise as therapeutic targets. These new technologies, which include certain transgenic lines, intravital imaging, optogenetic and chemogenetic actuators, in situ sequencing, scRNA-seq, and techniques for studying cell-cell interactions, have revealed environmental, microbial, and local factors that regulate various astrocyte subsets and, as a result, play significant roles in neurodegeneration. Additionally, some of these characteristics provide specific biological targets for neurological disease treatment. One of the biggest obstacles in the research is still connecting transcriptionally defined astrocyte subsets in real time with neuronal activity, behavior, and disease markers. The existence of functional subgroups with distinct roles in health and disease that exhibit notable variations among CNS regions, disorders, or disease states presents a major obstacle to the therapeutic targeting of astrocytes. It's interesting to note that several astrocyte-related mechanisms of disease pathogenesis are shared by several neurological illnesses, despite the identification of disease-specific astrocyte triggers and responses. Neurotoxicity and deficiencies in the regulation of extracellular glutamate levels, K+ ion recycling, or lactate shuttling are examples of cross-disease processes.

Targets for managing astrocyte-driven pathology in a variety of neurological disorders may be found in the pathways controlling these and other typical dysregulated astrocyte activities. However, in order to enable the therapeutic targeting of astrocytes, a number of basic questions need to be answered. To what extent are astrocyte subsets plastic and/or developmentally defined?

Moreover, which astrocyte subsets are shared between neurological diseases? What is their geographical distribution throughout the central nervous system? How can we find common pathogenic pathways and treatment targets by comparing astrocyte subsets across neurological disorders? Which experimental models are best suited for these subgroups' functional interrogation? Most critically, how can we target particular astrocyte subsets of interest therapeutically? These and other difficulties highlight the important functions of astrocytes in both health and illness, as well as their potential as useful targets for the management of neurological and neuropsychiatric conditions.

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