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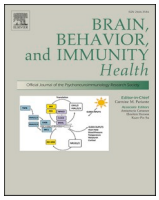

New perspectives on heterogeneity in astrocyte reactivity in neuroinflammation

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ABSTRACT

The inflammatory response is a fundamental aspect of all insults to the central nervous system (CNS), which includes acute trauma, infections, and chronic neurodegenerative conditions. As methods for investigating astrocytes have progressed, recent findings indicate that astrocytes can react to a diverse spectrum of insults affecting the central nervous system. Astrocytes respond to external and internal stimuli from the nervous system in a process called glial reactivity. Astrocyte reactivity, previously considered uniform and functionally inactive, is currently a very diverse event in different inflammatory processes. These differences can occur due to the nature, the intensity of the stimulus, the brain region involved and can range from subtle changes in astrocytic morphology to protein expression alteration, gene transcription profile shifts, and variations in the secretory pattern of molecules. The elucidation of the diverse roles of astrocytes in both normal and pathological conditions has led to increased interest in the notion that various astrocyte subtypes may exist, each contributing with distinct functions. Our study will prioritize the characterization of astrocytic response patterns in the context of the development and progression of neurodegenerative diseases, particularly Alzheimer's and Parkinson's. In addition, we will investigate the astrocyte's response during bacterial and viral infections, given the potential to enhance specific therapeutic interventions based on the reactivity profiles of astrocytes.

1. Astrocyte diversity

Astrocytes are classically divided into two major subpopulations in the cerebral cortex: fibrous astrocytes in the white matter and protoplasmic astrocytes in the gray matter. However, this classification is outdated considering the great diversity of astrocytes revealed by more detailed morphological and biochemical analyses (Schitine et al., 2015).

The classic markers of differentiated astrocytes are the glial fibrillary acidic protein (GFAP), calcium-binding protein S100β, glutamate–aspartate transporter and glutamate transporter 1 (GLT-1). However, astrocyte cells can assume distinct expression patterns regarding these markers. Several studies have shown morphologically distinct GFAP or S100β expressing astrocytes in varying proportions across different brain regions (Bachoo et al., 2004). Molecular assays using microarray gene expression profiles combined with multiple in vitro and *in vivo* astrocyte samples reveal relevant molecular heterogeneity among astrocytes in the normal adult brain that relies on their functional range in CNS physiology (Schitine et al., 2015; Emsley and Macklis, 2006; Bachoo et al., 2004; Escartin et al., 2021). Evidence indicates that GFAP immunolabels partially the total astrocyte volume and more than 40% of astrocytes were found to be GFAP-negative in the adult rat hippocampus (Walz and Lang, 1998). Additionally, GFAP is poorly labeled in protoplasmic human astrocytes and is expressed late in developing fibrous astrocytes (Bushong et al., 2002a,b). Regarding S100 β expression, this calcium-binding protein is also present in a subpopulation of mature oligodendrocytes, in the choroid plexus epithelial cells, and in a few neurons (Zhang et al., 2019). Therefore, these typical astrocyte markers can lead to an inaccurate investigation of astrocyte morphology and function.

NDRG2, a member of the N-myc downstream-regulated gene (NDRG) family, is a tumor suppressor and cell stress-related gene involved in cell differentiation and development (Shen et al., 2008). NDRG2 is highly present in the cerebral cortex, olfactory bulb, hippocampus, and thalamus. NDRG2 is also specifically found in astrocytes of

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the brain (Zhang et al., 2019). Thus, NDRG 2 could be a novel marker for non-reactive, non-proliferative astrocytes, however, the differences in its expression through the different brain areas or in other cellular contexts have not been addressed yet.

In conclusion, in defining astrocyte heterogeneity all sources of astrocyte phenotype should be considered and integrated with multi-dimensional statistical analyses. Translation assays from RNA or snRNA sequencing data to in situ immunohistochemical detection and functional validations are crucial because the molecular profiles of astrocyte clusters and subpopulations partly overlap. Thus, instead of individual markers, signatures composed of a combination of markers with specified levels of expression or relative fold changes are required to name astrocyte phenotypes (ESCARTIN et al., 2021; DAS et al., 2020)

2. Reactive astrocyte heterogeneity

The pathological contexts in which astrocyte reactivity occurs can markedly vary and may be sporadic or genetically mediated; acute or chronic; and due to a systemic pathology, specific injury, or disease of the CNS. By definition, astrocyte reactivity is a response to an extrinsic signal ranging from reversible alterations in gene expression and cell hypertrophy to scar formation with permanent tissue rearrangement. In addition, it is equivocating to equate simple and uniform measures such as cell hypertrophy and upregulation of GFAP expression with a single, uniform concept of astrocyte reactivity (Escartin et al., 2021; Anderson et al., 2014).

Glial fibrillary acidic protein (GFAP) is the most widely used marker of reactive astrocytes. The upregulation of GFAP mRNA and protein, as shown with multiple techniques including quantitative PCR (qPCR), RNA sequencing (RNAseq), in situ hybridization, electron microscopy, and immunostaining, is a prominent feature of many, but not necessarily all, reactive astrocytes (Escartin et al., 2021). Other characteristics need to be considered to establish astrocyte reactivity such as tissue reorganization, astroglial scar formation, changes in transcriptome profiles, degree of interaction availing interdigitation of cell processes, astrocyte proliferation levels, and the signaling profile mediating the astrocytes response. The broad range of molecular categories that can trigger reactive astrogliosis ranges from small molecules to large polypeptide growth factors and cytokines (Anderson et al., 2014). Some of these molecular mediators are released via specific signaling mechanisms leading to a wide variety of different intracellular signaling cascades and reflecting in the astrocyte reactivated profile.

While astrocytes exhibit certain shared characteristics in their responses to various pathological stimuli, their heterogeneity is significantly more intricate and dynamic than previously recognized. Reactive astrocyte populations should be characterized by a range of parameters, such as gene expression, proteomics, morphology, and functionality. Furthermore, the phenotype of astrocytes is influenced by their specific location within the central nervous system (CNS), the nature and progression of diseases, co-existing health conditions, age, sex, and other factors contributing to their diversity. Advanced techniques like high-throughput single-cell and single-nucleus RNA sequencing (scRNA-seq/snRNA-seq), along with spatial transcriptomics, have been extensively employed to elucidate the complex cellular composition of the CNS and to categorize various cell subsets. These cutting-edge methodologies also facilitate the identification of the diverse cell types and states that play a role in the development of brain disorders (Matusova et al., 2023).

In a pivotal transcriptomic investigation (Zamanian et al., 2012), delineated the various states of reactive astrocytes that arise during neuroinflammation and ischemic stroke in murine models subjected to bacterial lipopolysaccharide (LPS) injections and the middle cerebral artery occlusion (MCAO) technique. The study revealed that reactive astrocytes in both experimental conditions exhibited an upregulation of intermediate filament proteins, extracellular matrix components, adhesion molecules, regulators of metal ion homeostasis, and elements associated with immune response pathways. Notably, astrocytes activated by LPS displayed heightened immune response characteristics, whereas those activated by MCAO showed increased expression of genes linked to metabolic processes and cellular proliferation, likely related to neuroplasticity mechanisms following a stroke.

The reactive astrocytes induced by lipopolysaccharide and MCAO sometimes referred to as A1 and A2 subtypes (Liddelow et al., 2017; Escartin et al., 2021), have been classified as either detrimental/proinflammatory or beneficial/anti-inflammatory. However, this binary classification has been recognized as overly simplistic and inadequate to capture the true diversity of reactive astrocyte phenotypes (Escartin et al., 2021). These foundational studies have served as a valuable reference for subsequent research. In a more recent study (Leng et al., 2022), utilized single-cell transcriptomics to investigate the heterogeneity of astrocytes derived from human induced pluripotent stem cells (hiPSCs) that were treated with a cytokine combination previously established by Liddelow and colleagues in 2017. Their findings identified two distinct clusters of neuroinflammation-induced reactive astrocytes, with the IL-1/IL-6-responsive astrocytes (IRAS1) characterized by genes associated with the acute phase response, while the TNF/IFN-responsive astrocytes (IRAS2) demonstrated upregulation of interferon signaling pathways, highlighting their specialized roles.

In the next topics, we will focus on discussing the heterogeneity and the functional implications of astrocyte reactivity in a context-specific manner as regulated by specific signaling events such as infections and neurodegenerative diseases context.

2.1. *Bacterial infections*

Bacterial infections of the CNS are serious and often intractable conditions affecting the meninges and the brain parenchyma, that cause neurological dysfunction and are associated with high levels of inflammatory cytokines, especially IL-6 and TNF-α (Chauhan, S. V. et al., 2008). Despite the presence of receptors for pathogen-associated molecular patterns, diverse bacterial infections may exploit varied entry routes into the brain or engage in opportunistic approaches to infect the central nervous system. The interaction between various bacteria and astroglial cells is complex, in most cases the astroglial reactivity has a crucial role in the response to these infections.

2.2. *Pneumococcal meningitis (Streptococcus pneumoniae)*

Streptococcus pneumoniae it's a Gram-positive bacterium (Iovino, F. et al., 2013) commonly found on the nasopharynx and oropharynx mucosa of healthy individuals (Vieira, C. A. et al., 2007). It is the most common bacterial pathogen in cases of acute otitis media and pneumonia, and the second most important in cases of meningitis in children under 2 years of age. In the United States and Europe, 25–40% of meningitis cases are caused by this etiological agent (Vieira, C. A. et al., 2007). It was observed activation of astroglial reactivity on the meningitis cases caused by S. pneumoniae (Potokar, 2019). These meningitis cases are thought to be caused by pneumococci crossing the BBB and invading the CNS. Though Iba-1 and GFAP staining, researchers found that the microglia and astrocytes were activated as soon as 1-h post-infection, the immune response had a significant increase after 14 h post-infection (Iovino, F. et al., 2013). These results suggest that the microglia activation and astrogliosis did not lead to leukocyte recruitment at first and the CNS invasion by the bacterium is spatiotemporally separated (Iovino, F. et al., 2013).

2.3. *Meningitis (Neisseria meningitides)*

Astroglia reactivity occurs in infections with *N. meningitides.* There's also been compelling evidence to support the crucial role of endogenous substance P (SP) and neurokinin-1 receptor (NK-1R) interactions in the initiation and progression of central nervous system (CNS) inflammation

in vivo (Chauhan, S. V. et al., 2008). Suggesting, that the astroglial reactivity resulted in the increase of secretion of pro-inflammatory cytokines. This evidence where found through exposure to two clinically relevant bacterial CNS pathogens, namely Neisseria meningitidis and Borrelia burgdorferi. For Neisseria meningitidis, the study revealed that in mice genetically deficient in NK-1R expression or those treated with a specific NK-1R antagonist, there was a significant attenuation of *in vivo* elevations in inflammatory cytokine production. Moreover, a decrease in the production of an immunosuppressive cytokine was observed (Chauhan, S. V. et al., 2008). The researchers used isolated cultures of microglia and astrocytes to demonstrate that SP has the capacity to enhance inflammatory cytokine production in these resident CNS cell types when exposed to either of these bacterial pathogens. In conclusion, astroglial reactivity is evident in Neisseria meningitidis infections. Experiments with NK-1R-deficient mice and specific antagonists showed a significant attenuation of inflammatory cytokine production, emphasizing the potential modulation of CNS inflammation through these pathways (Chauhan, S. V. et al., 2008).

2.4. Viral infections

Viruses are categorized as neuroinvasive when they can enter the nervous system and neurovirulent when they can cause diseases within the nervous system. These terms describe the virus's ability to infiltrate and harm the nervous system (Potokar, 2019). Poliovirus is highly neurovirulent but weakly neuroinvasive, while rabies virus is highly neurovirulent and typically requires a traumatic entry point, such as an animal bite, for neuroinvasion. The immune response within the CNS is predominantly regulated by microglia and astrocytes. Since astrocytes have an important role in the BBB they are typically the first cell type in the brain to succumb to viral infections (Jorgacevski, J.; Potokar, M., 2023). Immune response can significantly impact the physiological and morphological aspects of cells and tissues. It is essential to carefully consider these changes, particularly in the context of persistent infections, as they may contribute to the emergence of recurring neurological consequences (Jorgacevski, J.; Potokar, M., 2023). Neurological consequences from virus infections in the CNS can also affect the development of babies in cases where the mother is infected.

2.5. Coronavirus 2019 (Covid-19)

The COVID-19 pandemic has reignited interest in neurotropic viruses, with astrocytes playing a pivotal role in responding to neurotrophic infections in the CNS, given that these viruses primarily target the BBB (Potokar, 2023). COVID-19 manifests a diverse range of symptoms, including significant neuroinfection, evidenced by alterations in astrocytes and microglia in post-mortem examinations of patients (Potokar, 2023). Studies highlight that astrocytes are the primary sites of viral infection in the CNS and that SARS-CoV-2 preferentially infects astrocytes in the brain through noncanonical mechanisms and that SARS-CoV-2-infected cells exhibit marked metabolic changes. SARS-CoV-2 infection in astrocytes may lead to neurological symptoms associated with long-term COVID-19, stemming from increased neuroinflammation and non-autonomous neuronal death (Huang & Fishell, 2022).

It's also been demonstrated that infection of astrocytes in brain organoids elicits a pathological response closely resembling reactive astrogliosis, marked by heightened production of type I interferon (IFN), amplified inflammation, and reduced expression of transporters responsible for water, ions, choline, and neurotransmitters (Kong, W. et al., 2022). The impact of these events within astrocytes creates a microenvironment that causes further dysfunctions and neuron cell death (Kong, W. et al., 2022). Another group has suggested that astrocytes are the main target of COVID-19, and infected astrocytes had a corresponding increase in reactivity characteristics, such as growth factor signaling and cellular stress (S). Elevated cytokines levels in astrocytes and microglia have been demonstrated for animal models as expected for an infection. However, in the central nervous system (CNS), microglia stand out as the primary contributors of cytokines such as interleukin 6 (IL-6), ultimately propelling the cytokine storm toward causing neuronal damage and the stimulation of astrocytes and microglial cells produce reactive oxygen species (ROS) (Chowdhury et al., 2021). These suggest that SARS-CoV-2 infection in astrocytes is marked by increased reactivity and cellular stress, accompanied by inflammatory effects, including heightened reactive microglia and a widespread loss of neurons via apoptosis. Astrocytes have a vital role in governing brain energy, metabolism, and the microenvironment. Noteworthy is the involvement of the protein BSG/CD147, crucial for astrocytic metabolic pathways and provides support for neuronal energy. Consequently, SARS-CoV-2 infection in astrocytes may indirectly contribute to neuronal death through inflammation and disturbances in brain energy metabolism (Huang, S. & Fishell, G., 2022). Exposure of astrocytes to pro-inflammatory cytokines, often induced by lymphocytes, can trigger the expression of pro-inflammatory genes, contributing to neuroinflammation and neurodegeneration. Activation of angiotensin receptor Type 1 (ATR1) on microglia leads to the release of NF-κB and pro-inflammatory cytokines, prompting a proinflammatory response in astroglia. The release of inflammatory markers by reactive astrocytes influences pathological outcomes. Elevated levels of glial fibrillary acidic protein (GFAP) in COVID-19 patients suggest that intrinsic inflammatory processes in the brain contribute to neuroinflammation (Huang, S. & Fishell, G., 2022). The neuroinflammatory substances from astrocyte reactivity can hinder axonal regrowth or contribute to enduring cognitive effects. Reactive astrogliosis serves the purpose of restoring the blood-brain barrier and ensuring neuronal survival. However, in certain pathways, such as Toll-like/NF-κB/STAT-3 signaling and pro-inflammatory microglial activation, astrocytes may undergo maladaptive reactive astrogliosis, turning them into cells with pro-inflammatory and pro-neurodegenerative characteristics (Huang, S. & Fishell, G., 2022).

Astrocytes undergo intricate changes in morphology, biochemistry, and function to activate the regenerative potential of the central nervous system. When the brain is not directly damaged, resolving systemic issues typically restores the physiological balance of neuroglial cells. However, the extent and dynamics of this process in pathological conditions are not well understood. In some cases, glial cells may not fully recover after infection, contributing to the development and progression of COVID-19-related neuropsychiatric disorders. Post-mortem examinations of COVID-19 patients' brains indicate alterations in both astrocytes and microglia. (STEARDO *et al.*, 2023). In summary, the consequences of COVID-19 infection on the brain, particularly in astrocytes, are still largely unknown. However, studies suggest a significant link between astrocyte reactivity and the neurological symptoms associated with COVID-19 (STEARDO *et al.*, 2023).

2.6. Human immunodeficiency virus (HIV/AIDS)

HIV infection in the CNS happens after primary infection and results in neurological complications, even in individuals using antiretroviral therapy (ART) (Eugenin, A. E. et al., 2011). The immunosuppression caused by HIV is also an important factor in the entry of pathogens in the brain; for example, *T. gondii* is a common opportunistic pathogen of the CNS in AIDS patients (Halonen, K. S.; Weiss M. L., 2000). Furthermore, AIDS has had a significant social impact in the last century. Therefore, it has seen a considerable amount of research. The mechanism of entry used by the HIV virus has been suggested to enter the astrocytes by endocytosis (Potokar et al., 2019). In HIV-1 infection, astroglia initially releases cytokines that impede viral replication. However, once infected, astrocytes produce viral proteins, including the membrane HIV-1 Tat protein, causing mitochondrial dysfunction and neuronal death. Microglial cells, through proinflammatory cytokine secretion, may further contribute to astrogliosis, potentially leading to abnormal

functions and neuronal damage (STEARDO *et al.*, 2023). Furthermore, it's been suggested that HIV disrupts the BBB by a mechanism gap junction-dependent (Eugenin, A. E. et al., 2011). A disruption of the BBB could explain why other infectious diseases are more prevalent in HIV patients. It's been suggested that the HIV virus also hijacks the cellular machinery in astrocytes to propagate its proteins to neighboring cells using vesicle-like structures (Potokar et al., 2019). Therefore, HIV infection in the CNS leads to neurological complications, persisting even with antiretroviral therapy.

2.7. Flaviviridae infections (Zika and dengue virus)

The Flaviviridae are a family of at least 66 viruses, 29 of which have been associated with human disease (Monath, T. P., 1990). Flavivirus infection in humans may lead to severe neurologic syndromes, and the pathogenic mechanisms behind these conditions are largely unknown (Mustafá, Y. et al., 2019). Therefore, it's important to understand these mechanisms for understanding how the Flaviviridae viruses infect the brain and the development of effective treatments. There are multiple species of Flaviviridae that infect humans and cause relevant diseases such as Tick-borne encephalitis virus (TBEV), Hepatitis C virus, Zika and Dengue virus. In this review, we focus on Zika and Dengue diseases due to their relevance and epidemic status in several countries (Veilleux, C. & Eugenin, E., 2023).

2.8. Zika virus (Zikv)

Zika virus epidemic in Central and South America. ZIKV is associated with a significant neurodevelopmental defect known as microcephaly, particularly in newborns born to infected mothers. The detrimental impacts of ZIKV on the developing brain result from the involvement of astrocytes at various stages of development. (Veilleux, C. & Eugenin, E., 2023). Additionally, in adults, ZIKV can induce neurological impairments, such as the Guillain-Barré syndrome, characterized by rapid-onset muscle weakness (Potokar, 2019). The ZIKV can enter astrocytes through endocytosis, which is a common mechanism of infection in multiple Flaviviridae. Following infection, astrocytes can become decisive in the replication of Zika virus when compared with other cell types (Jorgačevski et al., 2019). Making these cells is important for research into the disease. Considering this, astrocytes have a high basal expression of IFN-alfa and IFN-beta, type 1 IFNs that restrict viral growth (JORGACEVSKI, J.; Potokar, M., 2023). ZIKV strains differ in their sensitivity to the interferon (IFN)-induced antiviral response. The Asian ZIKV strain from Cambodia is more sensitive than strains from Uganda and Brazil (Tavcar et al., 2021).

During ZIKV infection, astrocytes have reportedly expressed IL-6, IL-8, IL-12, and IL-1alfa. Il-4 and TGF-beta1 (JORGACEVSKI, J.; Potokar, M., 2023). In primary cell cultures, astrocytes exhibited a greater susceptibility to ZIKV infection compared to neurons. They released a higher number of progeny viruses and demonstrated a greater tolerance for viral loads when compared to neurons. (Jorgačevski et al., 2019). These findings suggest that astrocytes have a definite role in the ZIKV infection. Another study found that astrocytes at early developmental stages are more susceptible to ZIKV infection than in the later stages of differentiation (Veilleux, C. & Eugenin, E., 2023). Apparently, ZKV doesn't compromise astrocyte apoptosis but increases neuronal apoptosis in a time-dependent and neurodevelopmental manner, during a specific developmental window (Veilleux, C. & Eugenin, E., 2023).

Regarding the impact of ZIKV on neurodevelopment, particularly focusing on astrocytic genes. In studies conducted RNA-seq analysis on ZIKV-infected Mouse Primary Astrocytes (MPAs). Genes such as GTP cyclohydrolase 1, lysyl oxidase, growth hormone receptor, leukemia inhibitory factor, and Rho-associated coiled-coil containing protein kinase 2 were upregulated in ZIKV-infected MPAs, whilst genes like myelin basic protein, oligodendrocyte transcription factor, achaete-scute family bHLH transcription factor 1, microtubule-associated protein tau, proteolipid protein 1, endothelin receptor type, notch 1, adenomatosis polyposis coli 2, signal transducer and activator of transcription 2, and complement component 3 were downregulated (Shereen et al., 2021) analysis of the RNA-seq data revealed that ZIKV infection could interrupt neurogenesis, neuron differentiation, development, migration, and maturation. Pathways affected included Hippo signaling pathway, focal adhesion, PI3K-Akt signaling pathway, and tight junction (Shereen et al., 2021). Additionally, studies in Human induced pluripotent stem cell (iPSC)-derived astrocytes found that ZIKV infection causes DNA breaks in astrocytes and DNA damage response signaling (Ledur et al., 2020). Consequences of ZIKV infection on astrocytes could have severe implications for brain development and neural progenitor migration. This information can contribute to understanding the mechanisms involved in ZIKV-associated neurodevelopmental disorders and may provide a basis for developing vaccines or treatments.

Flavivirus infection disrupts host transcriptomic profiles, numerous miRNAs have previously been associated with other flavivirus infections. In this context, a study has found that miR-17-5p is one of the most upregulated miRNAs in ZIKV infection, and it is a well-characterized miRNA in the regulation of the unfolded protein response, a pathway important for flavivirus replication (Kozak, R. A. et al., 2017). Strong NS1, and glycoprotein with an essential role in viral replication, and expression in astrocytes after 24–72 h of infection, was accumulated in vesicle-like structures in GFAP-positive cells. In older cultures infected there were fewer astrocytes containing NS1 protein. The results suggest that the NS1 expression and infection spread depend on the degree of astrocyte differentiation (Veilleux, C. & Eugenin, E., 2023). An early formation of viral structures after ZIKV infection accompanied by a significant compromise of intracellular structures was observed, including compromised ER, Golgi complex, vesicles, and the cytoskeleton. Nonetheless, the main effect seen was the extensive and large accumulation of virus within enlarged vesicles in conjunction with inter-organelle interaction dysfunction" (Veilleux, C. & Eugenin, E., 2023).

In conclusion, the Zika virus profoundly affects astrocytes, influencing viral replication, gene expression, and host transcriptomes. These insights highlight critical pathways for potential interventions to address the severe neurodevelopmental consequences of ZIKV infection.

2.9. Dengue virus (Denv)

The 4 different serotypes of Dengue virus (DENV) infect approximately more than 500 million humans annually (Calderón-Peláez et al., 2019), with 1–3% developing severe disease manifestations such as Dengue Hemorrhagic fever (DHF) and Dengue Shock syndrome (DSS). These manifestations are associated with vascular leakage and neurological sequelae (Lee et al., 2016). These findings suggest that DHF and DSS cases may have consequences for astrocytes that can be permanent in the patient. Even low-grade infection seems to induce measurable changes within the parenchyma of infected individuals (Lee et al., 2016). Astrocytes infection with DENV has been reported in fatal human biopsy cases. Therefore, astrogliosis could be involved in long-term complications presented in some patients, eventually leading to death (Calderón-Peláez et al., 2019). Despite that, limited studies on the effects of DENV infection on astrocytes present contradictory findings. Some studies use in vitro models and neuroadapted D4MB-6 dengue strains inoculation, which has a neurotropic and neurovirulent behavior (VELANDIA-ROMERO *et al.*, 2012). Reported no infection or detection of viral components in astrocytes (VELANDIA-ROMERO *et al.*, 2012). Moreover, no infection was observed when Balb/c astrocytes were exposed to strains of DENV2 and a strain of DENV4 (Imbert et al., 1994). However, generalized astrogliosis was observed in an *in vivo* model using Balb/c mice infected with the neuroadaptive strain D4MB-6. Particularly in younger mice with neurological symptoms, paralysis, and histopathological evidence of neuron infection. (Velandia-Romero et al.,

2012; Calderón-Peláez et al., 2019).

Strong or continuous stimuli can lead to significant astrogliosis, characterized by progressive cell hypertrophy and the development of longer and thicker astrocytic processes. This morphological transformation involves the overexpression of cytoskeleton proteins like GFAP, vimentin, and nestin, crucial for cell proliferation and glial scar formation (Lee et al., 2016). Viral-associated astrogliosis and hypertrophy have been reported to occur specifically in the white matter, suggesting a local immune activation with cell migration, down-regulated GFAP or cell death, causing cytoplasmic enlargement and an increase in the number and length of astrocytic end-feet in the white matter of *rhesus macaques* (Lee et al., 2016). There's also been reported the upregulation of miRNA-30e and miRNA-146a during DENV infection, generating an inflammatory response that is favorable for the virus. This corroborates with *in vivo* infection models and has also suggested important roles of miRNA in regulating infection and brain development (Kozak, R. A. et al., 2017).

Interestingly, older mice, refractory to infection and without neurological symptoms, still exhibited astrocytic activation, indicating that the immune and physiological development influences susceptibility to DENV infection and affects brain virus clearance.

Yet there are still questions about the duration of astrocyte activation, whether it returns to a normal phenotype after infection resolution or persists in the absence of the virus (Lee et al., 2016). Astrocytes may potentially respond to DENV by producing reactive oxygen species (ROS), a capability demonstrated by this cell type (Sheng. W. S. et al., 2013). Although not specifically investigated in this context, microglia have been observed to generate ROS in response to DENV infection, leading to encephalitis, a complication documented in patients infected with DENV (Suwanprinya, L. et al., 2017). Therefore, the astrocyte role in the DENV is still requiring more studies to understand the mechanisms and the extent to which the infection changes astrocyte activity.

3. Neurodegenerative diseases

Recent data has highlighted the contribution of glial cells to the pathophysiology of neurodegeneration (Matias et al., 2019). Both cellular senescence and neurodegeneration share pathological mechanisms such as a decline in cognition and memory, gliosis and astrocytic dysfunction (PALMER *et al.*, 2018).

Among the various complex functions associated with astrocytes in maintaining homeostasis and metabolic support of the central nervous system, they are crucial in synaptic regulation, astrocytic dysfunction probably contributes to or causes the loss of synapses and consequently, the cognitive decline observed in brain senescence and the progression of neurodegenerative diseases (Clarke et al., 2021; Matias et al., 2019).

The hippocampus and striatum are the brain regions most vulnerable to diffuse and severe neurodegeneration due to a greater expression of genes related to astrocyte reactivity (Anderson et al., 2014; Lee et al., 2022). Upregulation of one of the biomarkers for reactive astrogliosis, glial fibrillary acidic protein (GFAP), is detected in conditions of cellular senescence and late stages of neurodegenerative diseases (Lee et al., 2022; Zhou et al., 2019).

Astrocyte reactivity can be modulated by traumatic injury, ischemia, infection, cancer and neurodegenerative disease, and is also referred to as reactive astrocytes (Anderson et al., 2014; Gotoh et al., 2023). Work in the field of neurology has even indicated that microglial reactivity is followed by astrocytic reactivity in neurodegenerative diseases, showing that IL-10 and TGF-β signaling may be key in regulating these cellular interactions (Gotoh et al., 2023). Another study corroborates that astrocyte reactivity is initiated with the activation of the JAK/STAT3 pathway (Giovannoni et al., 2020).

Depending on the phase of cellular development and stimuli, reactive astrocytes present a duality in their neurotoxic or neuroprotective profile in neurodegeneration, and they can initially even positively modulate growth factors, anti-inflammatory cytokines and antioxidant enzymes (Andromidas et al., 2021). Despite this, the mechanisms of astrocytic reactivity, the interactions that astrocytes establish with other cells and the impact of regional heterogeneity are still a matter of discussion regarding the synaptic deficit and glial dysfunction implicated in the pathological process of neurodegeneration (Matias et al., 2019). Profile A1 astrocytes are present in the CNS tissue of elderly mice with neurodegenerative diseases, they express complement component 3, lose the ability to promote synaptogenesis and neuronal survival and induce the death of neurons through soluble neurotoxic factors modulated by molecules of microglial inflammatory signaling (Giovannoni et al., 2020; Escartin et al., 2019; Westergard et al., 2020).

In neurodegenerative diseases, clinical manifestations such as memory loss and mood disorders are caused by neuronal death, which, in turn, occurs in distinct patterns between brain regions due to regional glial heterogeneity (Lee et al., 2022). The loss of neuronal populations may occur, in part, due to failure in the functional heterogeneity of astrocytes in certain regions affected by the neurodegenerative disease (Clarke et al., 2021; Westergard et al., 2020). The regional heterogeneity of astrocytes may contribute to the mechanisms of neurodegeneration, probably as a response that depends on the type and chronicity of the stimuli (Clarke et al., 2021).

Recent studies suggest that heterogeneity in the expression profile of genes associated with astrocyte functions may predict the vulnerability of certain regions of the brain to neurodegenerative diseases, as well as brain senescence. The heterogeneity of astrocytes can be considered from different aspects, including the relationship with changes in regional identity, brain senescence and its correlation with molecular, morphological and functional levels (Matias et al., 2019).

There is a consensus among neuroscientists that the loss of normal cellular function is triggered by genetic, biological and environmental factors and reduces the ability to adequately maintain environmental homeostasis in the healthy central nervous system, affecting the physiology of cellular interactions and contributing to the state marked inflammatory process characteristic of the process of cellular senescence and neurodegeneration (Palmer et al., 2018).

In neurodegenerative diseases, a decrease in the density of astrocytes is observed in the initial stages of the pathology, as well as an increase in the number of senescent astrocytes with hypertrophic cellular processes and astrocytic cell death without self-renewal, as well as overlapping of astrocyte processes neighbours in more advanced conditions. In the senescent brain, astrocytes exhibit a secretory phenotype associated with a response to chronic inflammatory stimuli, becoming more reactive, in addition to the upregulation of vimentin and nestin as a response to neuronal damage (Anderson et al., 2014; Andromidas et al., 2021; Chen et al., 2023; Pekny et al., 2005).

Considering the contribution of astrocytes to the pathophysiology of neurodegeneration, it is essential to better understand the mechanisms that are related to CNS inflammation, more specifically reactive astrogliosis in neurodegenerative diseases such as Alzheimer's and Parkinson's.

3.1. Alzheimer's disease (Ad)

The neuropathology of AD has already been well elucidated in the literature and one of the characteristic mechanisms is the formation of amyloid beta (Aβ) plaques in the extracellular space and on the walls of blood vessels (Acioglu et al., 2021).

Several in vitro and *in vivo* studies report the role of astrocytes in the pathogenesis of AD. Dallérac et al. in 2016, presented the influence of astrocytes on cognitive and memory function through the regulation of genes that encode proteins associated with the extracellular matrix surrounding neurons. However, during the progression of AD, astrocytes can acquire toxic properties, losing mechanisms that facilitate the clearance of beta-amyloid, or that influence the protection of neurons against inflammatory effects caused by the accumulation of beta-amyloid, that is, losing their neuroprotective characteristics

(Acosta et al., 2017).

Recent studies, using RNA sequencing of astrocyte nuclei in an experimental model of AD in mice, were able to identify astrocytes with atrophic phenotypes during the initial phase of the disease, which worsens with the progression of the disease, being located around amyloid plaques, presenting a phenotype hypertrophic (Acioglu et al., 2021). Experimental models of AD in mice indicate a direct relationship between the association of astrocytes that acquired a hypertrophic phenotype in the final phase of the disease and the formation of amyloid plaques, considering that only astrocytes associated with amyloid plaques became hypertrophic (Zhou et al., 2019).

Data from Iadecola C. in 2004 and 2007 showed some damage-related vascular changes in the early stages of AD, including reduced blood flow. Later, the role of astrocyte integration in the neurovascular units that control vasoconstriction and vasodilation was also demonstrated. These studies corroborate a possible contribution of atrophic astrocytes observed in the initial phase of the disease to the damage to neurovascular units detected at the beginning of the disease, contributing to its progression (Zhou et al., 2019).

Ding in 2021, demonstrated that the inflammatory profile acquired by A1 astrocytes is also related to the deposition of Aβ, which induces the production and release of inflammatory mediators, such as cytokines, chemokines and ROS, resulting in neuronal damage. These inflammatory mediators also provide feedback to astrocytes, accelerating their activation, creating a vicious cycle and chronic inflammatory environment and contributing to the progression of AD (Ding et al., 2021). Acioglu et al. (2021) shows astrocyte-generated ROS induced by Aβ accumulation also exhibited harmful effects on cortical neurons. However, reactive astrocytes can exert biphasic effects (harmful or beneficial) in AD. For Ding et al. (2021), the protective capacity of reactive astrocytes in neurodegenerative processes associated with AD is presented when these cells can remove dystrophic neurites associated with amyloid plaque.

Reactive astrocytes can also express low levels of ROS, reaffirming their neuroprotective function. Furthermore, under physiological conditions, A0 astrocytes maintain a balance between ROS production and antioxidant generation (DING *et al.*, 2020). Other studies have also revealed the neuroprotective capacity of reactive astrocytes, which, by secreting antioxidant substances, protect neurons from toxic substances (Mcgann and Mandel, 2018). It is worth highlighting that an important characteristic in the pathophysiology of AD is the predominance of the phenotype of neuroinflammatory and neurotoxic astrocytes (A1) when compared to the number of astrocytes with an anti-inflammatory profile (A2) (Acioglu et al., 2021).

Alzheimer's disease (AD) is recognized as a highly diverse condition and is the leading cause of cognitive decline. Recent research has highlighted the significant involvement of non-neuronal cells in the initiation and progression of the disease. However, fully understanding their roles has proven difficult due to the variability among cell types and the dynamics of the disease itself. Recent advancements in single-cell or nucleus RNA sequencing have begun to characterize some of this cellular diversity, revealing disease-associated subsets of microglia in both mouse and human brains. In contrast, astrocytes, which exhibit a broad spectrum of activation states and have varying impacts on the onset and progression of the disease, remain less well characterized. Notably, substantial gliosis has been documented at the onset of AD, which has been linked to adverse effects. In a pivotal investigation characterizing astrocyte reactivity in Alzheimer's disease (AD), Andromidas et al. (2021) and Habib et al. (2020) conducted an analysis of the hippocampus in a transgenic mouse model utilizing single-nucleus RNA sequencing (snRNA-seq). The researchers identified two distinct clusters of astrocytes exhibiting elevated levels of GFAP expression, with one cluster being significantly more prevalent in the transgenic samples. These astrocytes were subsequently designated as disease-associated astrocytes (DAAs). While the DAAs shared some expression characteristics with GFAP-high astrocytes found in control samples, they uniquely upregulated genes associated with endocytosis, complement pathways, aging, and amyloid metabolism. Additionally, identifying homeostatic and intermediate astrocyte populations indicated the potential for dynamic transitions among individual astrocyte states. Similar DAA-like populations were also observed in the cortices of AD model mice and the brains of aged mice and humans (Acioglu et al., 2021; Matias et al., 2019), suggesting that this expression signature is not confined to a specific AD mouse model or brain region.

Taken together, such information may facilitate understanding the beneficial and detrimental mechanisms acquired by astrocytes that enhance or limit neurodegeneration in AD. Understanding the heterogeneity of astrocytes, identifying their specific phenotypes and subtypes in the disease becomes essential for the development of future therapeutic strategies that target reactive astrocytes in neurodegenerative disorders (Acioglu et al., 2021).

3.2. *Parkinson's disease (Pd)*

In addition to the diverse genes that are closely related to astrocyte biology and contribute to the pathophysiology of PD (Booth et al., 2017), the loss of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein in intracytoplasmic inclusions are some of the main pathological characteristics of PD (Balestrino and Schapira, 2020). However, the morphological changes of astrocytes in the progression of PD remain undefined (Zhou et al., 2019). In studies carried out on the substantia nigra and putamen of PD patients and analysis of GFAP labeling, low levels of astrogliosis were identified (Tong et al., 2015).

Analysis of experimental models of PD in monkeys detected a significant expansion of astrocytic processes of glutamatergic synapses in these animals. These studies suggest important implications for the structural changes of astrocytes in PD (Zhou et al., 2019).

α-synuclein is a soluble protein, found in presynaptic terminals in PD, it is associated with neurons in the substantia nigra, cortex and other structures in cytoplasmic inclusions (Acioglu et al., 2021). These studies identified astrocytes with accumulation of α-synuclein and demonstrated the capacity that these cells must absorb this protein released by axon terminals, however, intensive absorption can result in mitochondrial damage in astrocytes.

Acioglu et al. (2021) demonstrated in experimental models of PD in mice, that astrocytes with an A1 inflammatory profile were commonly observed, which secrete pro-inflammatory molecules, inducing dopaminergic neuronal death. Overexpression of α-synuclein also demonstrated a relationship with the release of chemokines and pro-inflammatory cytokines by reactive astrocytes, indicating the detrimental action of astrocytes in PD when induced by the accumulation of α-synuclein.

Other findings in the literature corroborate the relationship between the accumulation of α-synuclein in astrocytes and the gain of neurotoxic function of these cells (Di Domenico et al., 2019). These studies also suggest that, in the early stages of the disease, astroglial absorption of α-synuclein is a neuroprotective mechanism; however, as the concentration of this protein increases, astrocyte function becomes compromised. Therefore, the damage related to the loss of physiological function and gain of toxic function of astrocytes is characterized by the accumulation of α-synuclein.

Single-cell transcriptomics has been employed to analyze PD and Huntington's Disease (HD) (Ma and Lim, 2021; Malla et al., 2021); however, there has been limited research specifically targeting astrocytes. Additionally, other proteinopathies where astrocytes play a significant or causative role require further exploration, such as Alexander disease. The study conducted by Smajic et al. (2022) revealed the presence of CD44 high astrocytes in the midbrain of Parkinson's disease patients, the enrichment of astrocytes from these patients at the end of this activation pathway points to their potential role in the neuroinflammatory processes linked to Parkinson's disease. It is noteworthy

Table 1
Reactive Astrocytes and its Molecular Profiles according to each discussed disease (Aya, 2017; Chiu et al., 2020; Coureuil, 2012; Da silva et al., 2023; Edara et al., 2020; Farmen et al., 2021; Fu et al., 2022; Geyer et al., 2019; Kastenbauer et al., 2002; Kouli et al., 2018; Lutgen, 2020; Murta, 2020; Nassar et al., 2022; Ojha, 2019; Osborn et al., 2016; Raquel Esteves, 2009; Rizor et al., 2019; Sheppard and Coleman, 2020; Spurgat and Tang, 2022; Steardo Jr et al., 2023; Verkhratsky et al., 2015).

Type of Pathology	Category	Disease	Etiologic Agents	Mechanism	Astrocyte Activation Pathway	Astrocyte profile	Molecular Profile										References
							RNA (up-regulated)	RNA (down-regulated)	snRNAs (single nucleus RNAs)	miRNAs	Receptors	Cytokines	Interferons	Proteins	Peptides	Reactive oxygen species (ROS)	
Infectious Disease	Bacteria	Bacterial Meningitis	*Streptococcus pneumoniae*	via bloodstream with exact mechanism still up to debate	(PRR) pattern recognition receptors; TLR-2,NOD-2	Reactive Astrocytes expressing MHC class II and co-stimulatory molecules, such as CD80 (B7-1) and CD86 (B7-2)	-	-	-	-	toll-like 4 (TLR 4), TLR2, CD14	IL-1β, IL-6, TNF α, IL-6,IL-10 (in vitro), IL-1β TNF-α	-	MyD88	-		(GEYER, S. et al., 2019), (LIDDELOW et al., 2017), (VIEIRA, A. C. et al. 2007),(KASTENBAUER, S. et al.2002), (FARMEN, K. ET AL. 2021), (IOVINO, F. et al. 2013),(CHAUHAN, S. V. et al. 2008), (POTOKAR et al. 2019).
			Neisseria Meningitis	Primarily via paracellular traversal across the blood-brain barrier (BBB) or blood-cerebrospinal fluid barrier. Secondarially via the nerves that extend from the nasal cavity to the brain	(PRR) pattern recognition receptors; NOD-2, SR-MARCO, Complement-CD46	Reactive Astrocytes expressing MHC class II and co-stimulatory molecules, such as CD80 (B7-1) and CD86 (B7-2)	-	-	-	-	NK-1R	-	-	Substance P	present	(GEYER, S. et al., 2019), (COUREUIL, M. et al. 2012), (KASTENBAUER, S. et al.2002), (FARMEN, K. ET AL. 2021), (CHAUHAN, S. V. et al. 2008)
	Virus	COVID-19	Coronavirus 2019	Direct infection, Blood pathwa, Neuronal pathway, Immune-mediated injurypathway	Toll/NF-κB/STAT-3 signaling	Reactive Astrocytes recruiting peripheral Macrophages and Lymphocytes to the brain parenchyma.	-	-	SLC1A2, AQP4, CH3L1, GFAP, NCAM1, NCAM2, NRXN1	NRP1 mRNA, BSG mRNA	NRP1, BSG/CD147, Angiotensin receptor Type 1 (ATR1)	Cytokine Storm: IL-6, TNF-α, VEGF	IFN-α, IFN-β, IFN-γ	GFAP, NF-kB	-	present	(MURTA, V, et al. 2020), (SPURGAT, M. S., TANG, SHAO-JUN. 2022), (STEARDO JR, L. et al. 2023), (TAVCAR, P. et al.2021), (FU, Y. et al. 2022), (KONG, W. et al. 2022), (POTOKAR, 2023), (HUANG & FISHELL, 2022), (CHOWDHURY et al., 2021)
		HIV/AIDS	Human Immunodeficiency Virus	Gap junction-dependent BBB disruption	HDACs and SUV4K(3-9 silence HIV transcription in astrocytes	Reactive Astrocytes with enlarged vesicules abudant in viruses	-	-	-	mRNa-gag	Toot-like 3 (TLR3)	TNF-α	IFNγ, GM-CSF	HIV-1 Tat, Nef	-	present	(EDARA, V. et al. 2020), (LUTGEN, V. et al. 2020), (EUGENIN, E. et al. 2011)
		Flaviviridae Infections	Zika Virus	Crossing the Placental Barrier and BBB crossing by transcytosis, Cytokine-mediated BBB disruption, Endocytosis through Axl Receptor	Hippo Signaling pathway, Focal adhesion, PI3K-Akt Signaling pathway, Tight junction	Reactive Astrocytes with enlarged vesicules abudant in viruses, caspase independent cell death	TP cyclohydrolase 1, lysyl oxidase, growth hormone receptor, leukemia inhibitory factor, achaete-scute family bHLH transcription factor 1, microtubule-associated protein tau, proteolipid protein	myelin basic protein, oligodendrocyte transcription factor, Rho-associated coiled-coil containing protein kinase 2	-	miR-17-5p miRNA-30e,	Endothelin Receptor type, Notch 1 Receptor, Axl Receptor	IL-6, IL-8, IL-12, IL-1α, IL-4, TNF-α, TGF-β1	IFN-α, IFN-β	NS1 protein, GFAP, AP-1 transcription factors (JUN and FOS) GFAP,	-	-	(FEN CHIU, C *et al.* 2020), (da SILVA, E.V. et al. 2023), (OJHA, C. R. et al. 2019), (POTOKAR, M. et al. 2019), (SHEREEN, M. A.et al. 2021), (VEILLEUX, C. et al. 2023), (MUSTAFÁ, Y. et al. 2019), (LEDUR, P. et al. 2020), (KOZAK, R. et al. 2017), (MONATH, T. P., 1990) (LEE, K.M et al. 2016),(SUWANPRINYA, L. et al. 2017), (VELANDIA-ROMERO, M. et al. 2012), (MUSTAFÁ, Y. et al. 2019), (MONATH, T. P., 1990), (VEILLEUX, C. & EUGENIN, E., 2023), (CALDERÓN-PELAEZ et al., 2019), (IMBERT et al., 1994), (SHENG, W. S. et al., 2013)
			Dengue Virus	by binding with or without clathrin to endothelial cells and leukocytes	-	Reactive Astrocytes with Hyperthrophy	-	-	-	miRNA-146a	-	IL-6, TNF-α	IFN-β	Vimentin, Nestin	-	present	
Neurodegeneration		Alzheimer's Disease (AD)	Multifactorial Disease [both genetic (APP, PSEN1, PSEN2) and enviromental factors (Down Syndrome, Cardiovascular Disease, Diabetes, Inflammation, Pollution, Stress, Heavy metal exposure)]	Accumulating amyloid β / inducing the spread of tau pathology	JAK / STAT3, PI3K / AKT (Hippocampus) pathway	Reactive Astrocytes with A1 (inflammatory) profile toxic properties, atrophic and/or hypertrophic phenotypes	-	-	GFAP, CD44, CLU,NEAT1, CH3L1, MT2A, MT1E, CRYAB, HSP90AA1, HSPA1A, HSPB1 LINGO1, RASGEF1B	miR-155, miR-181a, miR-132, miR-218, miR-124, miR-466, miR-669, miR-3082-5p, miR-297a-5p, miR-146a, miR-146b,	TREM2, Pgp,GLUT1, LDLR, LRP-1	IL-10, TGF-β, IL-6, TNF-α	IFN-β, IFN-γ	GFAP, BACE-1, Amyloid beta (Aß), Complement component 3	-	present	(SHEPPARD O. et al. 2020), (SPURGAT, M. S., TANG, SHAO-JUN. 2022) (VERKHRATSKY, A. et al. 2015), (AYA U., et al. 2017), (OSBORN, L. et al. 2016)
		Parkinson's Disease (PD)	Multifactorial Disease [both genetic (SNCA,PINK1, LRRK2) and enviromental factors (Smoking, Caffeine, Pesticides)]	Loss of neurons dopaminergics in the substantia nigra and the accumulation of ɣ-synuclein	JAK / STAT3 pathway	Astrocytes with ɣ-synuclein accumulation and A1 profile (inflammatory)	-	-	GFAP, CD44, CLU,NEAT1, CH3L1, MT2A, MT1E, CRYAB, HSP90AA1, HSPA1A, HSPB1	miR- 153, miR- 223, miR-200a-3p, miR-326, miR-330 and miR-3089	NOD2,	IL-10, TGF-β, TNF-α, IL-1β, PGE-2, iNOS	IFN-γ	GFAP, α-synuclein, Complement component 3	-	present	(KOULI A. et al. 2018), (RAQUEL ESTEVES, A. et al. 2009), (SPURGAT, M. S., TANG, SHAO-JUN. 2022), (TONG, J. et al. 2015), (AYA U., et al. 2017), (RIZOR, A. et al. 2019), (NASSAR, A. et al. 2022), (MATUSOVA, Z. et al.2023)

that, similar to the observations made by Habib et al. (2020), the study also found GFAP-high astrocytes in control groups, indicating that astrocyte heterogeneity is present even in healthy individuals. In summary, the findings from the studies on Parkinson's disease (PD), Huntington's disease (HD), and Alzheimer's disease (AD) demonstrate the existence of similar reactive astrocyte populations across multiple neurological disorders.

Therefore, researchers must gain a better understanding of the molecular and cellular interactions that take place during the development and progression of neurodegenerative diseases. This knowledge will lead to the screening and development of safe and effective treatment approaches, as well as potential preventative measures. It may also lead to the prevention, delay, interruption, or reversal of neurodegeneration.

4. Conclusion

Astrocytes are highly heterogeneous cells in terms of morphology, receptor expression, molecule secretion, cellular metabolism and gene expression. To summarize, detail and facilitate understanding of the possible markers expressed by the different astrocytic reactivity profiles that these cells can assume in different neuroinflammatory contexts, we prepared a table with the data discussed in the work (Table 1). This diversity begins during the early stages of development, where cells in the neural tube are exposed to different types and concentrations of morphogens, generating domains that will lead to glial differentiation and specification. The presence of different subpopulations of astrocytes suggests that these cells respond to physiological and pathological stimuli may also be very heterogeneous. Several recent studies discussed in this work show that depending on the type, nature or duration of stimulus, injury or pathogen, specific endogenous signaling pathways can be activated, leading to a pattern of astrocytic reactivity that is very particular to the environmental context.

Therefore, it is very important to investigate astrocytic reactivity profiles, analyzing cellular, metabolic changes, protein and gene expression patterns, as well as studying the dynamics of the progression of astrocyte reactivity for a more comprehensive understanding of diseases and thus obtaining substrates to create new possibilities and targets for therapeutic approaches in various diseases, such as infections and neurodegenerative diseases.

CRediT authorship contribution statement

Daniel Evangelista Santos: Writing – review & editing, Writing – original draft, Investigation. **Sarah Alexandra Silva Lima:** Writing – review & editing, Writing – original draft, Investigation. **Leticia Santos Moreira:** Writing – review & editing. **Silvia Lima Costa:** Formal analysis. **Clarissa de Sampaio Schitine:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization.

Declaration of Competing interest

The authors declare no conflict of interest.

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Data availability

No data was used for the research described in the article.

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