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Interaction between Microglia and Mitochondrial Metabolism in the Development of Amyotrophic Lateral Sclerosis (ALS)

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons, leading to muscle weakness and eventual paralysis. Although the precise mechanisms driving ALS are not yet fully elucidated, emerging evidence suggests a crucial role of neuroinflammation and mitochondrial dysfunction in disease progression. Microglia, the brain's resident immune cells, play a central role in the neuroinflammatory response and undergo metabolic reprogramming during ALS, shifting from a homeostatic state to an inflammatory one. This reactivity is linked to mitochondrial dysfunction, which impairs energy production but allows microglia to maintain a pro-inflammatory phenotype through alternative pathways, such as glycolysis. This interaction between mitochondrial metabolism and microglial function exacerbates neuroinflammation, contributing to neuronal damage and accelerating ALS pathology. Mutations in genes like C9ORF72, SOD1, and TARDBP, commonly associated with ALS, also affect cellular processes such as RNA metabolism and mitochondrial function, further worsening the effects of the disease. This review explores the role of microglial mitochondrial metabolism in ALS, highlighting its importance in disease progression and identifying potential therapeutic targets to modulate neuroinflammation and metabolic dysfunction to slow ALS progression.

KEYWORDS: Amyotrophic Lateral Sclerosis (ALS), Mitochondrial dysfunction, Neuroinflammation, Metabolic reprogramming

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is the third most common neurodegenerative disorder, following Alzheimer's and Parkinson's diseases (Vahsen *et al.*, 2021). It is a heterogeneous neurodegenerative disease primarily characterized by the degeneration of upper motor neurons, which extend from the cortex to the brainstem and spinal cord, and lower motor neurons, which project to muscles. This leads to motor and extra-motor symptoms, with progressive muscle weakness being the most prominent feature (Hardiman *et al.*, 2017). ALS affects 1 to 2.6 individuals per 100,000 annually, with the onset typically between 58 and 60 years of age (Talbott, Malek e Lacomis, 2016). Survival following diagnosis ranges from 2 to 4 years, and due to population aging, ALS cases are expected to increase by nearly one-third in the next decade (Arthur *et al.*, 2016). This rising prevalence underscores the urgent need to gain deeper insight into the underlying mechanisms of ALS, including the role of immune responses and neuroinflammation in disease progression.

The brain is an immunologically active organ with an innate and adaptative immune system. Microglia are one

of the brain's primary immune cells, responsible for maintaining cerebral homeostasis and protecting neuroimmune environment while also playing a key role in neurodegenerative processes (Scheiblich *et al.*, 2020; Wang, Q. *et al.*, 2022). In diseases such as ALS, neuroinflammation triggers metabolic reprogramming in these cells, shifting them from a homeostatic resting state to a reactive one. Neuroinflammation refers to the cellular and molecular processes that involve the activation of microglia and astrocytes and the infiltration of peripheral immune cells. Recent genetic and imaging studies, primarily clinical, indicate that microglia are essential in driving neuroinflammation and subsequent pathology of ALS. These findings are supported by pre-clinical studies that utilize animal and *in vitro* models to replicate human disease, providing a foundation for the molecular understanding of ALS(Ashford *et al.*, 2021; Wang, M.-J. *et al.*, 2022). Growing evidence shows that this reprogramming is linked to energy, lipid, and iron metabolism, with microglia rapidly altering their energy metabolism to adapt to the neurodegenerative environment (Wang, Q. *et al.*, 2022).

Mutations in over thirty genes and loci have been associated with ALS. Still, the most affected are C9ORF72, SOD1, TARDBP, and FUS. While these mutations are not specific to microglia, they are linked to disruptions in RNA metabolism and translational biology, as well as mitochondrial dysfunction and oxidative stress (Cook e Petrucelli, 2019; Falabella *et al.*, 2021; Mathis *et al.*, 2019). These mutations disrupt several key cellular pathways, including RNA processing, protein homeostasis, axonal transport, and mitochondrial function, all contributing to neurodegeneration (Lewinski e Keller, 2005; Weishaupt, Hyman e Dikic, 2016).

Emerging studies suggest that the interaction between microglia and mitochondrial metabolism plays a crucial role in the progression of neurodegeneration in ALS. Mitochondrial dysfunction in microglia impairs energy production but paradoxically allows these cells to sustain a reactive phenotype, potentially via alternative metabolic pathways like glycolysis. This sustained reactivity exacerbates neuroinflammation, worsening ALS pathology. Rather than resolving inflammation or clearing debris, as seen in Alzheimer's, reactive microglia in ALS may amplify neuronal damage by releasing pro-inflammatory cytokines and ROS, marking a key point of disease progression (Harvey *et al.*, 2024; Neel *et al.*, 2023). Understanding how these metabolic alterations in microglia contribute to neuronal damage offers promising avenues for identifying therapeutic targets aimed at slowing or halting the progression of the disease. Despite advances in understanding its molecular basis, ALS remains a fatal disease with no cure, highlighting the importance of continued research into its pathogenesis and possible therapeutic targets.

Physiopathology of ALS

The clinical presentation of ALS is heterogeneous, depending on the regions of the brain or spinal cord affected. Symptoms usually begin in a localized area but gradually spread to adjacent regions of the neuroaxis. Upper motor neuron involvement leads to weakness, spasticity (muscle rigidity), and loss of motor control in the limbs, while degeneration of lower motor neurons results in muscle atrophy, cramps, and fasciculations (involuntary muscle contractions) (Brown e Al-Chalabi, 2017). In some cases, the disease begins with dysfunction of the bulbar nuclei, responsible for various vital functions of the body. As a result, the clinical manifestations include progressive dysarthria (speech difficulties), followed by dysphagia (difficulty swallowing), breathing problems, facial muscle weakness, and emotional instability (Hardiman *et al.*, 2017).

ALS can be classified into familiar (10% of cases) and sporadic (90%) forms. Familial ALS is often associated with other neurological conditions, such as frontotemporal dementia, while the causes of sporadic ALS remain largely unknown. Regardless of form, ALS leads to progressive motor neuron loss and muscle atrophy, with the involvement of both upper and lower motor neurons typically having shorter survival, especially when progressive bulbar palsy is present, which can reduce survival to 1-4 years from diagnosis (Grad *et al.*, 2017).

Diagnosing ALS is challenging due to the variability in clinical presentation and the similarity of early symptoms with other conditions, such as neuropathies or vascular disorders, which often leads to delays and misdiagnoses (Bradford e Rodgers, 2024). Electromyography is a key diagnostic tool, with active (AD) and chronic (CD) denervation serving as markers of disease progression and physiological disability (Colombo *et al.*, 2023). ALS diagnosis is confirmed clinically by observing motor neuron dysfunction in the absence of an alternative explanation, supported by imaging and electromyography (Ilieva, Vullaganti e Kwan, 2023). Advanced techniques, such as MRI and biomarker analysis in body fluids, further aid in diagnosis (Xu e Xu, 2024).

A significant feature of ALS is the neurodegeneration of the medulla oblongata, which is responsible for speaking and swallowing functions. Dysarthria and dysphagia are common and can appear either in the disease or during its progression (Yunusova *et al.*, 2019). The Revised ALS Functional Assessment Scale (ALSFRS-R) is widely used to assess bulbar function, including speech, swallowing, and salivation (Plowman *et al.*, 2017). Cognitive and behavioral symptoms may also arise, particularly in cases associated with frontotemporal dementia. These impairments can affect information processing, emotional regulation, memory, and social interactions, further complicating disease management (Rusina, Vandenberghe e Bruffaerts, 2021).

The pathophysiology of ALS involves disruptions in several molecular pathways, including autophagy, which plays a central role in the disease. Mutations in key genes, such as superoxide dismutase 1 (SOD1) and ubiquitin 2 (UBQLN2), contribute to the pathogenesis of ALS. Mutations in SOD1, which normally protects neurons from oxidative damage, lead to toxic protein aggregation and oligodendrocyte degeneration, compromising myelin production and disrupting nerve signal conduction. Similarly, mutations in UBQLN2 impair damaged proteins' degradation, causing abnormal protein aggregate accumulation, which induces cellular stress, mitochondrial dysfunction, and neuroinflammation, particularly in motor neurons (Nguyen, Thombre e Wang, 2019).

Microglia and neuroinflammation

Microglia are the primary immune cells involved in neurodegenerative and inflammatory pathogenesis in the central nervous system (CNS). These cells originate from primitive myeloid progenitors, specifically from macrophages derived from the yolk sac, which appear before the eighth embryonic day and invade CNS (Ginhoux *et al.*, 2010). Studies show that microglia can recruit monocyte-derived macrophages by producing attractive factors such as the chemokine monocyte chemoattractant protein-1 - MCP-1 (CCL2) a common outcome in various neuroinflammation contexts (**Figure 1**). This suggests that without microglia activity, there would be a delay in the macrophage response within the CNS (Brennan *et al.*, 2022). The CCL2 chemokine acts through a binding axis to the CC chemokine receptor type 2 (CCR2) and 4 (CCR4) receptors, thereby promoting macrophage recruitment (Pan *et al.*, 2020).

Another factor that supports the infiltration of macrophages into the CNS is the reduction in monocyte levels in peripheral blood in cases of ALS (Mantovani *et al.*, 2009). Studies indicate that in an inflammatory brain environment with degenerating neurons, the integrity of the blood-brain barrier is compromised, allowing peripheral immune cells into the CNS. This breakdown of the blood-brain barrier can be attributed to factors such as endothelial cell degeneration, perivascular edema, and capillary leakage (Garbuzova-Davis e Sanberg, 2014).

One theory currently under investigation regarding communication between cells from different environments involves extracellular vesicles (EVs), which can carry information such as nucleic acids, proteins, and metabolites. This interaction can alter the microenvironment and influence disease progression (Berumen Sánchez *et al.*, 2021). EVs can cross the blood-brain barrier and enter the bloodstream or modify its structure. In this manner, cells from different environments can communicate via extracellular vesicles as mediators following a stimulus. This cell signaling facilitates macrophage recruitment to the brain, contributing to the inflammatory and degenerative state (Saint-Pol *et al.*, 2020). Thus, the interplay between glial cells, EVs, and macrophages may represent a crucial mechanism for recruiting immune cells to the brain and promoting ALS pathogenesis.

In the pathological context of ALS, both resident and infiltrating macrophages play significant roles. Initially, they exhibit a protective, but later, they shift to a degenerative and inflammatory role in the advanced stages of the disease. Consequently, macrophages not only perform their natural phagocytic functions but also promote cytokine release as part of the immune response (Rios *et al.*, 2021).

Crosstalk Between Neurons and Microglia

Activated microglia present two distinct phenotypes: neurotoxic and neuroprotective. The first one corresponds to pro-inflammatory (activated via the classical pathway) and anti-inflammatory (activated via the alternative pathway) responses (Lyu *et al.*, 2021). Classically activated microglia exhibit a cytotoxicity profile characterized by the production of reactive oxygen species (ROS) and the release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-12, and tumor necrosis factor (TNF)-α (Colonna e Butovsky, 2017; Liddelow *et al.*, 2017). Furthermore, excessive pro-inflammatory activation can lead to a phenotypic transition from alternative to classical microglia, which increases neurotoxicity and contributes to a more severe progression of disease (Kwon e Koh, 2020).

Conversely, activated microglia exhibit neuroprotective activity through the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β (Butovsky *et al.*, 2014). They also produce fibroblast growth factor (FGF), colony-stimulating factors (CSF1), and neuronal growth factor (NGF) and stimulate the phagocytosis of misfolded proteins and cellular debris (Saijo, Crotti e Glass, 2013). Initially, activated microglia plays a neuroprotective role at the onset of ALS; however, as the disease progresses, there may be a shift from a neuroprotective to a neurotoxic profile (Liao *et al.*, 2012). The polarization of microglial profiles in ALS is multifactorial, influenced by damage-associated molecular patterns (DAMPs), neuronal damage-associated molecular patterns (NAMPs), as well cytokines, chemokines, and oxidative stress(Shi e Zhu, 2023; Tortelli *et al.*, 2020).

In ALS, neuroinflammation is mediated by misfolded proteins resulting from mutations primarily in Transactive response DNA-binding protein 43 (TARDBP), RNA-binding protein fused in sarcoma/translocated in liposarcoma (FUS), chromosome 9 open reading frame 72 (C9orf72), and superoxide dismutase type 1 (SOD1) (Berdyński *et al.*, 2022; Hao *et al.*, 2020; White *et al.*, 2018). Additionally, mutations in multifunctional proteins involved in innate immune responses, along with variations in cytokine and chemokine receptors, can promote an initial pro-inflammatory activity characteristic of a classically activated microglial profile

(Cognata, La *et al.*, 2024). However, despite this initial pro-inflammatory state, crosstalk between neuronal cells can facilitate the transition to an alternative microglial profile, thereby reducing neuroinflammation. For example, microglia produce IL-10, which binds to IL-10R receptors on astrocytes, prompting them to secrete TGF-β and polarizing microglia towards an anti-inflammatory profile (Norden *et al.*, 2014). In contrast, healthy neurons in an inflammatory environment also contribute to the reduction of inflammation through the release of CD200 and fractalkine (CX3CL1). These molecules attenuate microglial activation via CD200r and CX3CR1 receptors, promoting a more anti-inflammatory profile at the onset of the disease through the secretion of IL-4, insulin-like growth factor (IGF)-1, Brain-derived neurotrophic factor (BDNF), and IL-10 (Béland *et al.*, 2020; Inoue *et al.*, 2021; Yi *et al.*, 2012).

Additionally, chronic DAMPS stimuli, such as protein aggregates, exogenous ATP, and cellular debris, bind to receptors like tool-like receptors (TLRs), purinergic receptors, and triggering receptor expressed on myeloid cells 2 (TREM2) on microglial cell membranes and can drive the transition from an anti-inflammatory to a pro-inflammatory profile (Calovi, Mut-Arbona e Sperlágh, 2019; Colonna, 2023; Fiebich *et al.*, 2018). This reduces negative co-stimulation, typically mediated by C-X3-C Motif Chemokine Ligand 1 (CX3CL1) and OX-2 membrane glycoprotein (CD200), and promotes the increased release of pro-inflammatory factors such as TNF-α, IL-1β, IL-6, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Ultimately, this cascade triggers neuronal degeneration on a large scale (Fan *et al.*, 2023; Hickman *et al.*, 2018).

Metabolic Reprogramming in Neuroinflammation

Under homeostatic conditions, microglia function as sentinel cells in the brain, using glucose as their primary energy source for adenosine triphosphate (ATP) production (Bernier *et al.*, 2020). Glucose is internalized into the microglial cytoplasm via GLUT transporters and metabolized through oxidative phosphorylation (OXPHOS). In this process, glucose initially undergoes glycolysis, producing pyruvate and lactate. Pyruvate, in turn, can also enter the mitochondria to form acetyl-CoA and initiate the tricarboxylic acid (TCA) cycle, ultimately generating ATP via OXPHOS (Caputa, Castoldi e Pearce, 2019). Alternatively, glucose may be metabolized via the pentose phosphate pathway, generating nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), which can lead to the production of ROS and components that support nucleotide synthesis, facilitating phagocytosis (Gimeno-Bayón *et al.*, 2014). However, in pathological conditions affecting the brain, such as ALS, microglia demonstrate the ability to utilize other substrates for energy production (Fairley, Wong e Barron, 2021).

In a neuroinflammatory environment, microglia undergo metabolic reprogramming towards a pro-inflammatory profile, favoring glycolysis as their primary energy source (Vandoorne, Bock, De e Bosch, Van Den, 2018). This shift in metabolites increases NADH levels, promoting the formation of C-terminal binding protein (CtBP) dimers, which results in the release of p300, an acetyltransferase that acetylates subunit p65 of nuclear factor kappa-beta (NF-κB). This acetylation triggers the release of pro-inflammatory cytokines TNF-α and IL-6 (Shen *et al.*, 2017). Conversely, hypoxia induces a different response. During hypoxia, there is an increase in the transcription and activity of hexokinases, which convert glucose into glucose-6-phosphate. This process is accompanied by the upregulation of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), further promoting glycolysis and resulting in elevated levels of pyruvate and acetyl-CoA. While the specific TCA cycle metabolites that accumulate in microglia remain unclear, evidence from pro-inflammatory macrophages suggests that similar metabolites – such as citrate, succinate, fumarate, malate, and oxaloacetate – may also accumulate in microglia (Jha *et al.*, 2015; O'Neill e Pearce, 2016). Additionally, evidence suggests that pro-inflammatory microglia stimulate the mTOR-HIF-1α axis, leading to an increased expression of GLUTs transporters and enhanced transcription of pro-inflammatory cytokines mediated by activator protein 1 (AP-1) and NF-κB (Bernier, York e MacVicar, 2020; Christoforidou, Joilin e Hafezparast, 2020) (**Figure 1**).

As previously mentioned, under homeostatic conditions, microglia primarily utilize the OXPHOS pathway for energy production. However, in pro-inflammatory environments, metabolic reprogramming tends to shift toward glycolytic pathways. Evidence suggests that in ALS, mutations in SOD1 and C9orf72 contribute to this shift towards glycolysis and a reduction in OXPHOS activity. This shift is driven by the upregulation of hexokinase-2, lactate dehydrogenase, mTOR, and the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, polarizing microglia toward a neurotoxic phenotype (Miao *et al.*, 2023).

While little is known about anti-inflammatory metabolic reprogramming in ALS, it is established that neuroprotective microglia decrease glycolysis and increase OXPHOS, thereby reducing ROS production and promoting the expression of 5'-prime-AMP-activated protein kinase (AMPK), which modulates a neuroprotective phenotype through the stimulation of IL-4, TGF-β, signal transducer and activator of transcription 3 (STAT3), and IL-10. Additionally, evidence suggests that beta-oxidation of fatty acids, regulated by the activation of proliferator-activated receptors (PPARs) and liver X receptors (LXRs), supports the use of fatty acids as an energy source and helps maintain lipid homeostasis. This process reduces ROS production and encourages the

maintenance of a neuroprotective phenotype (Wang, Q. *et al.*, 2022).

Impact of Mitochondrial Dysfunction in Glial Cells on ALS Progression

Under physiological conditions, the CNS, which includes astrocytes, oligodendrocytes, microglia, and ependymal cells, exhibits compartmentalized metabolic activity to ensure its proper functioning. The CNS relies on key metabolites, such as glucose, glutamate, and ketone bodies, as energy substrates (Vandoorne, Bock, De e Bosch, Van Den, 2018). Glucose supports the glycolytic pathway, the TCA cycle, and the OXPHOS chain, providing ample energy support to maintain CNS functions (Yu *et al.*, 2024). Adequate oxidation of glutamate plays a critical role in protecting neurons from excitotoxic cell death (Divakaruni *et al.*, 2017). Additionally, the metabolism of ketone bodies ensures CNS functionality during periods of glucose deprivation, allowing the system to maintain homeostasis and meet neural demands (Vandoorne, Bock, De e Bosch, Van Den, 2018).

From the neuroimmunometabolic perspective, cells such as astrocytes and neurons exhibit different preferences for metabolic substrates. Neurons demonstrate a lower glycolytic rate under homeostatic conditions due to the continuous degradation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), a positive modulator of the glycolytic pathway, mediated by the anaphase/cyclosome E3 ubiquitin ligase (APC/C) promoter complex - CDH1 (Bolaños, Almeida e Moncada, 2010). This leads to a reduction in glycolytic activity and an increase in oxidative potential, particularly the robust functioning of the oxidative phosphorylation chain(Bolaños, Almeida e Moncada, 2010; Vandoorne, Bock, De e Bosch, Van Den, 2018). Furthermore, in neurons, glucose serves as a crucial substrate for the activation of the pentose phosphate pathway (PPP). By increasing the concentration of glucose-6-phosphate (G6P) and subsequently activating the PPP, glucose enables the regeneration of reduced glutathione, thereby ensuring the antioxidant capacity of neurons (Vandoorne, Bock, De e Bosch, Van Den, 2018). With an adequate supply of reduced glutathione, continuous neuroprotective activity is maintained, which helps preserve mitochondrial membrane potential ($\Delta\psi m$) and prevents neurons from undergoing apoptosis or, in some cases, neurodegeneration (Herrero-Mendez *et al.*, 2009).

Meanwhile, astrocytes, which possess high-affinity glucose transporters (GLUT1), exhibit greater glycolytic activity compared to neurons (**Figure 2**). The enzyme PFKFB3 is active in astrocytes, facilitating extensive glycolysis and, consequently, high lactate production (Magistretti e Allaman, 2015). This elevated lactate production is further supported by the widespread expression of lactate dehydrogenase, specifically the LDH5 isoform, and pyruvate dehydrogenase kinase 4, which inhibits the activity of pyruvate dehydrogenase (PDH), thereby reducing pyruvate synthesis and reprogramming the cellular metabolic state to enhance lactate production (Halim *et al.*, 2010). The lactate produced by astrocytes is then transported to neurons via monocarboxylate transporter 4 (MCT4), present in astrocytes, and absorbed by monocarboxylate transporter 2 (MCT2), present in neurons. Subsequently, neurons utilize this metabolic intermediate to continue the oxidative process, generating ATP and ensuring metabolic support for various neuronal components, including the soma, synapses, and nodes of Ranvier (Bouzier-Sore *et al.*, 2006; Vandoorne, Bock, De e Bosch, Van Den, 2018).

Oligodendrocytes, in turn, play a crucial role in the metabolic support of the axonal regions associated with the myelin sheath, particularly in motor neurons(Philips e Rothstein, 2017). Specifically, oligodendrocytes exhibit high expression levels of monocarboxylate transporter 1 (MCT1), which facilitates the transport of lactate, ketone bodies, pyruvate, and H^+ ions across the plasma membrane according to their concentration gradient towards the neurons, utilizing MCT2 transporters (Pierre *et al.*, 2000), as seen in figure 2. In this way, oligodendrocytes help maintain the metabolic state of neurons by supplying energy, particularly in the form of lactate, through transporters such as MCT1, thereby promoting the proper functioning of neural structures (Lee *et al.*, 2012).

Astrocyte Metabolic Reprogramming in ALS: A Link to Neuroinflammation and Neuronal Death

Astrocytes, derived from induced pluripotent stem cells (hiPSCs), are glial cells of fundamental importance, as they enable the metabolic supply to motor neurons. Thus, a close link can be established between astrocyte mitochondrial activity and neuronal survival (Cassina *et al.*, 2021). In the pathogenesis of ALS, there is widespread metabolic dysfunction in astrocytes, commonly associated with the SOD1 mutation (Martinelli *et al.*, 2025). This leads to the activation and release of cytokines such as CXCL1, IL-6, and IL-8, which in turn promote the activation of the transcription factor associated with inflammatory processes, NF-κB. This process corroborates the triggering of cell-autonomous reactive transformation, resulting in the metabolic reprogramming of astrocytes and contributing to the development of the neuroinflammatory stage observed in ALS (Taha *et al.*, 2022).

In the pathogenesis of ALS, SOD1 mutant astrocytes exhibit neurotoxic behavior, primarily targeting motor neurons which are initially affected due to their metabolic vulnerability and high energy demand.(Díaz-Amarilla *et al.*, 2011). This neurotoxicity is attributed to morphometric changes in astrocytes, which can promote irreversible neural damage by recruiting Bax-dependent cellular machinery (a pro-apoptotic protein), leading to neuronal death via

apoptosis (Nagai *et al.*, 2007). Additionally, these astrocytes enhance the expression of the glial fibrillary acidic protein (GFAP) promoter, particularly in the ventral horn, which is atrophied due to the drastic degeneration of motor neurons (Mastrangelo *et al.*, 2023). SOD1 mutant astrocytes also impair lactate transport to neurons, resulting in metabolic dysfunction and a deficit in neuronal ATP production, thereby exacerbating the characteristic neuronal death seen in ALS (Ferraiuolo *et al.*, 2011).

This ATP deficit leads to the disruption of cellular ionic gradients, promoting hyperexcitability, prolonged depolarization, and neuronal death due to ATP depletion. The insufficient supply of lactate to neurons is the primary cause of increased axonal hyperexcitability, exacerbating degeneration and the progression of the disease. This hyperexcitability can also lead to overactivation of the ATPase-dependent Na^+-K^+ pump, resulting in increased ATP consumption and subsequent cell death due to ATP depletion, generating a positive loop (Ngo e Steyn, 2015). Therefore, astrocytes play a significant role in the development of ALS particularly in the context of SOD1 mutations. The alteration of their physiological function, particularly regarding the proper transport of lactate to neurons, results in metabolic deficiency and exacerbates the neural degeneration characteristic of ALS (Lee *et al.*, 2012).

Mitochondrial Dynamics in ALS: Implications for Microglial Activation and Neuronal Viability

Although microglial function is essential for the survival of motor neurons, studies involving bone marrow-derived microglia transplantation have shown that the elimination of macrophages using clodronate liposomes increased the survival of neurons in the CNS (Honda *et al.*, 2022). However, when this transplantation prioritized the acquisition of M2-type microglia, there was an improvement in ALS prognosis in mice (EPPERLY *et al.*, 2019). In this context, a reduction in the expression of pro-inflammatory genes, such as Nos2 and IL-6, was observed, alongside an increase in anti-inflammatory genes, such as Arg1 and Mrc1 (Kobashi *et al.*, 2022). This indicates that macrophage-mediated inflammation, potentially from the M1 subpopulation, may accelerate ALS progression (Dyke, Van *et al.*, 2016).

Molecularly, therapy with dimethyl fumarate and H-151, compounds with anti-inflammatory activity, has been reported to reduce pro-inflammatory cytokines such as IL-1β, IL-6, IL-15, IL-23A, and IFN-γ, potentially indicating the activation of the cGAS-STING pathway(Zamiri *et al.*, 2023). However, the role of microglia in the development of ALS remains inconsistent. Regarding signaling molecules produced by microglia, while some studies cite the involvement of insulin-like growth factor 1 (IGF1) in promoting microglial invasion in the sciatic nerve and improving inflammation in ALS (Ji *et al.*, 2018), other studies point to macrophage migration inhibitory factor (MIF1), a pro-inflammatory cytokine previously recognized as a chemoattractant, which now appears to have a new role as a chaperone (Leyton-Jaimes, Kahn e Israelson, 2018). The chaperone activity of MIF1 is particularly important for its ability to reduce protein aggregates formed in the cytoplasm (Basile *et al.*, 2020); in this context, the delivery of MIF1 in adult SOD-ALS mice via adeno-associated virus (AAV) delayed disease progression and increased survival (Alfahel *et al.*, 2024). Interestingly, the role of MIF1 as an adjuvant in ALS progression is closely linked to mitochondrial activity, as mitochondria are responsible for releasing the apoptosis-inducing factor (AIF), which binds to MIF1, directing it to the cell nucleus where it induces genomic DNA fragmentation and subsequent cell death (Park *et al.*, 2020).

Spatially, microglia in ALS patients tend to concentrate in the motor cortex and subcortical white matter (Togawa *et al.*, 2024). The stimulation of the RAGE (Receptor for Advanced Glycation End Products) receptor in microglia is associated with increased macrophage infiltration, as this receptor is also present in neurons and astrocytes. Deletion of RAGE in microglia in male ALS models has been shown to delay disease progression, highlighting the importance of this receptor in the pathogenesis of ALS (MacLean *et al.*, 2021). Biomarkers such as chitotriosidase have been identified as potential indicators for the stratification of ALS patients (Steinacker *et al.*, 2018), reflecting the presence of pro-inflammatory macrophages that produce pro-inflammatory cytokines, thereby influencing gluconeogenesis, lipolysis, and fatty acid oxidation (Martinez-Merino *et al.*, 2018). Similarly, advanced glycation end products (AGEs) are also described as being closely linked to ALS progression, contributing to pro-inflammatory macrophage infiltration and subsequent neuronal death (MacLean *et al.*, 2021).

Mitochondrial dysfunction is closely linked to ALS. Mutation in C9orf72 gene for instance, one of the most observed mutations in ALS, impairs the OXPHOS pathway, particularly by hindering the efficient assembly of complex I of the phosphorylation chain (Wang *et al.*, 2021). Complex deficiency I can increase the $NADH/NAD^+$ ratio, decrease TCA cycle activity, and elevate the AMP/ATP ratio. The excess AMP leads to increased phosphorylation of AMPK, which inhibits the mechanistic target of rapamycin complex 1 (mTORC1) pathway (Straub, Weraarpachai e Shoubridge, 2021). In this context, dysfunction in autophagy, particularly in C9-ALS, has been associated with the prevention of lysosomal vesicle fusion with the autophagosome (Corrionero e Horvitz, 2018), further impairing the degradation of dysfunctional mitochondria. Additionally, mitochondrial dysfunction characterized by increased oxidative stress, mitochondrial fragmentation, and altered mitochondrial connectivity can be mitigated by treatment with the pTau-S396 protein, primarily linked to microtubule

structure (Petrozziello *et al.*, 2022). A more robust cellular transport structure can enhance various cellular processes that promote cell health, such as vesicle transport and autophagy, thereby preventing the accumulation of dysfunctional mitochondria that contribute to premature cell death (Petrozziello *et al.*, 2022), improving nucleus-cytoplasmic communication (Mann *et al.*, 2023), and facilitating mitochondrial motility through the axonal space for more efficient energy delivery (Esperante *et al.*, 2024).

Unlike the predominantly ALS-promoting functions of macrophages, oligodendrocytes exhibit significant neuroprotective activity by providing physical and energetic support to neurons. Demyelination is often cited as a contributing factor to ALS progression (Minj, Upadhayay e Mehan, 2021; Yusuf *et al.*, 2022). In this context, a pro-inflammatory profile is critical for the loss of oligodendrocyte viability. Unlike multiple sclerosis, which has a more direct etiology related to myelination and autoimmune characteristics, in ALS the activation of the STAT3 and mTOR pathways, coupled with a reduction in the PPARγ pathway, has been linked to increased remyelination and improvements in behavioral, motor, and cognitive functions, along with reduced neuroinflammation (Kumar *et al.*, 2024). This association with the inflammatory profile is further supported by observations of improved ALS prognosis in patients treated with Acetyl-11-keto-beta Boswellic Acid (AKBA), a potential activator of the Nrf2/HO-1 pathway, which offers neuroprotective effects (Minj, Upadhayay e Mehan, 2021). Additionally, viral elements integrated into the human genome, particularly HERV-K, are implicated as significant contributors to oligodendrocyte death, primarily through necroptosis mediated by Mixed-Lineage Kinase Domain-Like protein (MLKL) (Curzio, Di *et al.*, 2020).

Oligodendrocytes have been identified as important early markers of ALS, particularly in individuals exhibiting motor symptoms, showing signs of activation even before astrocytes or microglia (Golia *et al.*, 2024). This activation is attributed to signaling through EVs. Furthermore, exposure of the human oligodendrocyte cell line, MO3.13, to cerebrospinal fluid (CSF) from ALS patients has been shown to reduce their viability, primarily by decreasing the production of neuroprotective factors such as glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) (Ramya *et al.*, 2023). Similarly, myelin-forming cells in the peripheral nervous system (PNS), known as Schwann cells (SCs), also provide protective support to neurons; SCs offer special protection against oxidative stress-induced damage by producing peroxiredoxin-1 (Yamamuro-Tanabe *et al.*, 2023). Conversely, SCs have been implicated in exacerbating ALS, particularly through the activation of the c-KIT receptor in macrophages via the production of colony-stimulating factor 1 (CSF1) and interleukin 34 (IL-34), which is crucial for the increased infiltration of pro-inflammatory macrophages into the nerve (Trias *et al.*, 2020).

In addition to the connection between mitochondria and inflammation, particularly when mediated by ROS, mitochondria are also closely associated with protein synthesis. In this context, the physical connection between mitochondria and the endoplasmic reticulum (ER) via mitochondria-associated membranes (MAM) facilitates signaling in response to diminished mitochondrial metabolism, which can lead to ER stress by disrupting Ca^{2+} signaling (Zhu *et al.*, 2024). Additionally, improvements in ER stress have been associated with the modulation of the c-Jun N-terminal kinase (JNK) pathway, a crucial regulator of apoptosis, resulting in neuroprotection (Bos *et al.*, 2019). Furthermore, the reduction of mitochondria has been identified as an indicator for axonal reduction and demyelination (Esperante *et al.*, 2024) although its role in ALS remains to be established.

In summary, mitochondrial activity is crucial in the progression of ALS, primarily by inducing pro-inflammatory states in microglia, reducing energy supply from astrocytes, and compromising neuronal structures by impairing oligodendrocyte function. Mitochondrial dysfunction is primarily characterized by the accumulation of amyloid protein structures in the mitochondrial membrane, dysfunctional assembly of oxidative phosphorylation complexes, and the persistent production of ROS. These factors collectively lead to a metabolic shift from OXPHOS to glycolytic pathways, resulting in progressive neuronal death over time.

Pathological mechanisms associated with mitochondrial dysfunction in ALS

Mitochondria are the primary organelles responsible for energy synthesis (through ATP synthesis) and are significantly affected by increases in intracellular ROS. The elevation of ROS leads to mitochondrial dysfunction, which can indicate the degree of neuropathic progression in ALS. One of the first mechanisms observed in ALS is the inappropriate intracellular elevation of sodium (Na^{+}) and calcium (Ca^{2+}) cations during neuronal stimulation. These characteristics are similar to those observed in other neuronal disorders, such as long-term neurodegeneration in Alzheimer's disease, Parkinson's disease, and Huntington's disease (Zündorf e Reiser, 2011). This cation imbalance results in reduced ATP synthesis, which, in turn, exacerbates ROS production, impairing the OXPHOS pathway and causing further mitochondrial damage, ultimately leading to neuronal death (Anoar, Woodling e Niccoli, 2021). Mitochondrial dysfunction contributes to cell death via both intrinsic and extrinsic apoptotic pathways. In the intrinsic pathway, the release of proteins from mitochondria activates caspase-3, while in the extrinsic pathway, the binding of

specific ligands to FAS and DR6 receptors activates caspase-8, resulting in apoptosis (Jhanji *et al.*, 2021).

In molecular terms, a reduction in the activity of complexes I, II, III, and IV of the electron transport chain leads to decreased ATP concentration(Vandoorne, Bock, De e Bosch, Van Den, 2018). Complex I of the oxidative phosphorylation pathway oxidizes NADH, resulting in the reduction of ubiquinone in the inner mitochondrial matrix. The energy generated during this process is essential for the translocation of protons across the membrane, contributing to the establishment of a negative membrane potential. Additionally, the leakage of electrons during this process to oxygen contributes to the increased synthesis of cellular superoxide. While the exact mechanism underlying the dysfunction of complex I remain unclear, it is known that ROS induces oxidative stress, which damages proteins and adversely affects the functionality of complex I (Ghiasi *et al.*, 2012).

ALS impacts the CNS in ways that disrupt energy metabolism, ultimately leading to neuronal death. Notably, glycolysis is reduced during the symptomatic stages of the disease in both the cortex and spinal cord. This reduction can be demonstrated using radioactive carbon (C^{13}) in glucose, revealing decreased levels of cytosolic metabolites derived from glucose in the early and intermediate stages of ALS. Additionally, the decline in the neurotransmitter gamma-aminobutyric acid (GABA) in the spinal cord correlates with the reduction in glycolytic activity. The deficiency of essential metabolites required for the TCA cycle results in decreased levels of branched-chain amino acids and tyrosine, highlighting the CNS's energy demands in the context of the disease. Furthermore, in cases of neuronal metabolic dysfunction or motor neuron death, there is a reduction in N-acetyl-aspartate (NAA) levels; the spinal cord utilizes this substrate to meet its energy metabolism needs (Tefera e Borges, 2019). Aspartate, an excitatory neurotransmitter, serves as a potential biomarker for ALS progression. In the early stages of the disease, serum levels of aspartate are either decreased or remain normal; however, in chronic stages, an increase in aspartate and GABA levels has been observed, resulting in an excitatory-inhibitory imbalance that contributes to reduced patient survival (Jordan *et al.*, 2018).

In ALS, neuronal degeneration is largely attributed to neurotoxicity caused by elevated levels of ammonia, which results from dysfunctions in the hepatic urea cycle, crosses the blood-brain barrier and accumulates in neurons, ultimately leading to neurodegenerative processes (Parekh, 2015). During states of hyperammonemia, a risk factor for sporadic amyotrophic lateral sclerosis (ALS), there is a notable reduction in ATP production in the brain due to decreased levels of high-energy phosphates, which inhibits proton transport to the malate-aspartate shuttle. High concentrations of ammonia lead to the deactivation of the Na^+/K^+-ATPase pump, resulting in increased sodium and intracellular water influx. This causes tissue swelling, particularly in astrocytes, along with proteolysis, mitochondrial degradation, and the production of ROS (Gropman, Summar e Leonard, 2007). Astrocytes play a critical role in recovering glutamate (Glu) by converting it into glutamine (Gln) through the ATP-dependent enzyme glutamine synthetase (GS) (Yuan, Zhang e Li, 2017). The excess glutamine in the mitochondria of astrocytes is subsequently metabolized into NH_4 and Glu by the mitochondrial enzyme phosphonoacetate gamma-aminotransferase (PAG) (Zielińska, Albrecht e Popek, 2022).

The exacerbated synthesis of glutamate, responsible for the excitation of motor neurons, results in cell damage. In ALS, and different neurodegenerative diseases, GABA and glycine are the main inhibitory molecules counteracting glutamatergic effects (Diana *et al.*, 2017; Ramírez-Jarquín e Tapia, 2018). Glutamate-mediated excitotoxicity arises from the exacerbated influx of Ca^{2+} into motor neurons by the ionotropic receptor activated by glutamic acid (Caioli *et al.*, 2013) (**Figure 3**). The inhibition of GABAergic receptors leads to a decrease in Mg2+, which results in opening the NMDA receptors, a process that facilitates the entrance of Ca2+, which when in excess promotes neuronal death (Hou *et al.*, 2020; Sunico *et al.*, 2011).

The Intersection of Genetic Mutations and Energy Metabolism in ALS: Implications for Biomarker Discovery

ALS is a progressive neurodegenerative disease with a familial origin in 10-15% of cases (Marchi, De *et al.*, 2023). Among the more than thirty genes and loci associated with its pathogenesis, most exhibit dominant inheritance, although some display autosomal recessive characteristics (like SOD1 and FUS) and X-linked inheritance (such as UBQLN2) (Mathis *et al.*, 2019). In this context, genetic factors seem to influence the mutation frequency in ALS. In the Asian population with familial ALS, a significant proportion of causative mutations are found in SOD1 (30%), FUS (6.4%), and other known and unknown genes (59.8%). In contrast, Europeans often exhibit mutations in C9ORF72 (33.7%), SOD1 (14.8%), and other genes (44.5%) (Veldink, 2017).

Mitochondrial damage, as mentioned before, is a significant factor in ALS development (Cozzolino *et al.*, 2013), particularly due to its role in reducing ATP production and increasing oxidative stress, both of which affect motor neuronal functions (Miquel *et al.*, 2012; Szelechowski *et al.*, 2018). Superoxide dismutase is a crucial antioxidant enzyme that protects cells from ROS by converting superoxide into oxygen and hydrogen peroxide. Reduced levels or mutations affecting their catalytic activity can have serious phenotypic consequences (Azadmanesh e Borgstahl, 2018). This misfolding and aggregation of this enzyme are well-documented in familial ALS cases (Saccon *et al.*, 2013), often occurring due to sumoylation or oxidation (Fei *et al.*, 2006;

Trist *et al.*, 2022). In addition to ROS, the erroneous disulfide bond breakage or the loss of metal cofactors also contributes to misfolding, affecting pathology (Tsekrekou *et al.*, 2024). This "prion-like" behavior of SOD1 has been described as contributing to the spread of motor neuron degeneration through corticospinal pathways (Ayers *et al.*, 2016). However, recent studies have shown that genetic ablation of the $SOD1^{G373}$ transgene in corticospinal neurons is associated with protection against degeneration without affecting the mutant SOD1 load in the spinal cord (Scekic-Zahirovic *et al.*, 2021).

ALS also affects neuronal cell signaling. In this context, glutamate-mediated excitotoxicity is considered a potential pathogenic mechanism (Mathis *et al.*, 2019). Oxidative stress and dysregulation of iron metabolism in ALS patients and animal models with SOD1 mutations lead to excessive glutamate efflux, glial cell toxicity, and disturbances in calcium homeostasis (Hayashi, Homma e Ichijo, 2016). Regarding energy supply, motor neurons are particularly sensitive to even small reductions in energy and rely heavily on ATP for intracellular biochemical processes (Mathis *et al.*, 2019). Consequently, the diminished functionality of sodium-potassium pumps (due to decreased ATP levels) results in slow depolarization and hyperexcitability (Mathis *et al.*, 2019). This condition is exacerbated by persistent sodium channels, leading to increased intracellular calcium levels and subsequent apoptosis(Le Masson, Przedborski e Abbott, 2014).

FUS regulates the transcription of SOD2, an essential antioxidant located in the mitochondria, thereby linking oxidative stress with motor neuron dysfunction (Dhar *et al.*, 2014). Additionally, FUS is involved in RNA processing and transcription regulation, and its fusion with CHOP contributes to tumor development (Brumbaugh-Reed, Aoki e Toettcher, 2024). The first ALS cases associated with FUS were described in the early 2000s (Vance *et al.*, 2009), where impaired stress granule responses due to FUS mutants were identified as a factor contributing to motor neuron dysfunction (Li *et al.*, 2013). The formation of cytoplasmic FUS inclusions, which resemble stress granules and contain temporarily inactive RNAs and translation proteins, promotes cell survival under stress by redistributing translation resources (Mathis *et al.*, 2019). Many familial ALS mutations are located on chromosome 16, leading to aberrant localization of FUS (from the nucleus to the cytoplasm) and the formation of protein inclusions (Gal *et al.*, 2011). This suggests two possible pathogenic mechanisms: impairment of FUS's normal nuclear function and toxic cytoplasmic accumulation (Yang *et al.*, 2014). Toxicity may be influenced by PP2A and GSK3; a genomic screening study using Drosophila motor neurons linked the loss of function or inhibition of these proteins to FUS-associated lethality, which rescued significant disease phenotypes in mice and ALS patient motor neurons (Tziortzouda *et al.*, 2024). Understanding the correlation between genetic background and energy metabolism is crucial for identifying biomarkers and developing strategic therapies for ALS prevention and/or control in both familial and sporadic forms (Burg e Bosch, Van Den, 2023).

Moreover, C9ORF72, located on chromosome 9 (9p21), is a key gene related to monogenic forms of ALS. Its pathogenic mutation involves an abnormal hexanucleotide repeat expansion (G4C2) in the gene's first intron (Sellier *et al.*, 2024). Following DNA damage, the C9ORF72 protein is rapidly recruited to double-strand break sites, where it regulates genetic repair via the DNA-PK complex and initiates DNA damage response signaling (He *et al.*, 2023). In ALS, C9ORF72 mutations lead to the formation of secondary structures with expanded hexanucleotide repeats (HRE), which create stable G-quadruplexes in both DNA and RNA (Sellier *et al.*, 2024; Su *et al.*, 2014). The formation of G4C2 repeats generates RNA foci that bind to expanded DNA repeats, disrupting genomic stability and transcription (Lee *et al.*, 2013; Sellier *et al.*, 2024). RNA neurotoxicity likely arises from these foci sequestering essential RNA-binding proteins (RBPs), impairing RNA regulation and causing cellular dysfunction (Sellier *et al.*, 2024).

G4C2 (or G2C4) repeat expansion can also translate into repetitive dipeptide proteins (DPRs) observed in the motor neurons of ALS patients. Toxic DPR polyGA activates programmed cell death and TDP-43 cleavage, establishing a link to ALS (Lee *et al.*, 2013; Sellier *et al.*, 2024). In vivo, the expression of DPR significantly reduces with DDX3X overexpression, resulting in the absence of neuroinflammation or neurotoxicity (Fu *et al.*, 2024).

TAR DNA-binding protein 43 (TDP-43), encoded by the TARDBP gene on chromosome 1 (1p36.22), binds both DNA and RNA (Wang e Sun, 2023). This nuclear ribonucleoprotein is essential for RNA splicing, gene transcription regulation, mRNA stability, biosynthesis, and nuclear body formation (Kametani *et al.*, 2016), frequently altered in familial ALS (Meyer, 2021). Neurodegeneration in ALS is likely caused by either a toxic gain of function and abnormal TDP-43 or a loss of normal TDP-43 function, as aggregated TDP-43 is characterized by improper phosphorylation, truncation, and cytoplasmic mislocalization (Mathis *et al.*, 2019). TDP-43 undergoes liquid-liquid phase separation, contributing to the formation of stress granules (SGs) associated with RNA metabolism and the cellular stress response (Song, 2024).

UBQLN2, linked to the X chromosome, plays a role in protein degradation via the ubiquitin-proteasome system (Renaud *et al.*, 2019). Pathogenic mutations in UBQLN2 promote the formation of amyloid-like aggregates, contributing to neurotoxicity (Sharkey *et al.*, 2018). TBK1 kinase, which is involved in autophagy and innate immunity, phosphorylates substrates such as OPTN and p62, which are critical for selective autophagy in ALS (Mathis *et al.*, 2019).

Loss of function or mutations in TBK1 increase the risk of ALS and disrupt interferon responses in microglia and astrocytes (Cui *et al.*, 2018). TBK1 mutations also attenuate the interferon response in microglia and astrocytes, potentially slowing neurodegenerative progression and enhancing motor neuron survival (Mayl e Sreedharan, 2020).

In conclusion, the relationship between genetic mutations and energy metabolism in ALS reveals the complexity of the disease and its potential for biomarker discovery. Mutations in key genes, such as SOD1, FUS, C9ORF72, and TDP-43, alter metabolism and neuronal functions, as well as contribute to mitochondrial dysfunction, oxidative stress, and dysregulation of bioenergetic homeostasis. These factors ultimately lead to the degeneration of motor neurons and the progression of ALS. Understanding the mechanisms underlying these mutations and their cellular impacts is essential for advancing our understanding of the disease.

CONCLUDING REMARKS

In this review, we summarize the knowledge on how the interaction between microglia and mitochondrial metabolism contributes to the development and progression of ALS. This interaction between microglia and the neurodegenerative environment, mediated by metabolic alterations, appears to be a key factor in the pathogenesis of ALS, suggesting that modulation of mitochondrial metabolism may represent a promising target for therapeutic interventions.

The genetic mutations associated with this disease, such as C9ORF72, SOD1, TARDBP, and FUS, reveal critical cellular pathways involved in the pathology, including RNA metabolism, oxidative stress, and mitochondrial dysfunction. However, more studies are needed to fully elucidate how these mutations affect the interaction between microglia and mitochondria and how this can be exploited for the therapy's development.

In the future, research into the link between microglia and mitochondrial metabolism could open new frontiers in ALS treatment. Interventions aimed at mitigating metabolic responses in microglia have the potential to slow disease progression and improve patients' quality of life. Therefore, ongoing research into the cellular and molecular mechanisms underlying ALS remains crucial for advancing therapeutic innovations.

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Figure Legends

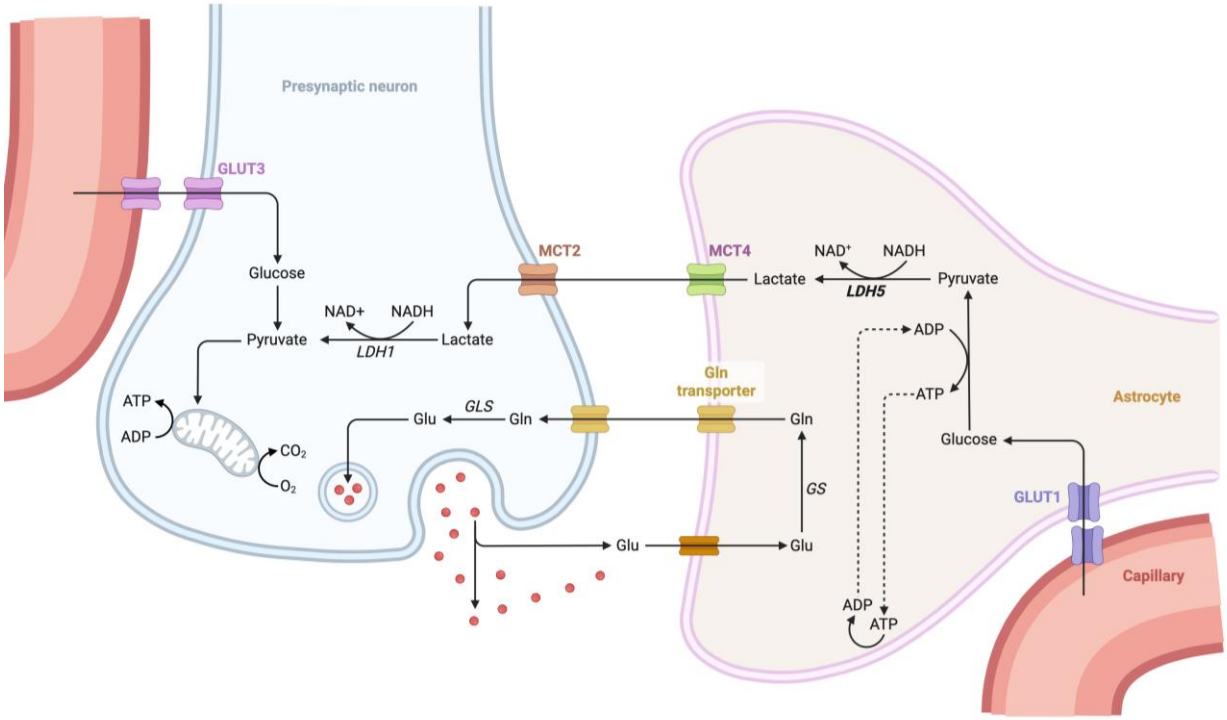

Figure 1. **Metabolic state of pro-inflammatory microglia in neuroinflammation**. In states of neuroinflammation, such as ALS and other neurodegenerative conditions, microglia adopt a pro-inflammatory profile, favoring glycolysis as their primary energy source while reducing their dependence on oxidative phosphorylation (OXPHOS). This increase in glycolysis elevates nicotinamide adenine dinucleotide (NADH) levels, promoting C-terminal-binding protein 1 (CtBP) dimer formation and releasing p300, which acetylates NF-κB, resulting in the expression of pro-inflammatory cytokines. Hypoxia exacerbates glycolysis, increasing pyruvate and acetyl-Coenzyme A (acetyl-CoA) levels. Additionally, the mammalian target of rapamycin (mTOR) - hypoxia-inducible factor-1α (HIF-1α) pathway is activated, enhancing glucose uptake and amplifying nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated cytokine production. While these metabolic changes are observed in ALS, they represent a more general mechanism that occurs in various neurodegenerative conditions.

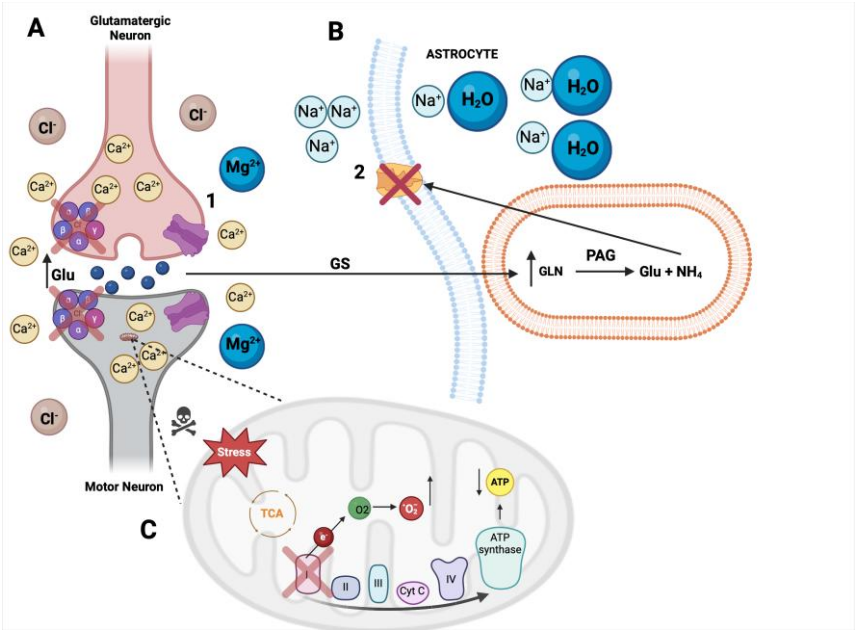

Figure 2. Under physiological conditions, there is extensive interaction between astrocytes and the metabolic support of neurons. Glucose from blood capillaries enters the astrocyte via glucose transporter protein type 1 (GLUT1) and is metabolized through the glycolytic pathway until it is converted to lactate by the enzyme lactate dehydrogenase (LDH) isoform 5 (LDH5). This lactate is then transported to the neuron via monocarboxylate transporter 4 (MCT4) presents on the astrocyte membrane and subsequently taken up by monocarboxylate transporter 2 (MCT2) on the neuron. The lactate is then converted back to pyruvate, allowing the continuation of the tricarboxylic acid cycle (TCA) and the oxidative phosphorylation pathway, thereby ensuring an adequate metabolic supply for neurons. Glu – glucose; Gln – Glutamine; GLS - Glutaminase; GS - The α subunit of stimulatory G protein-coupled receptor; ADP – adenosine diphosphate.

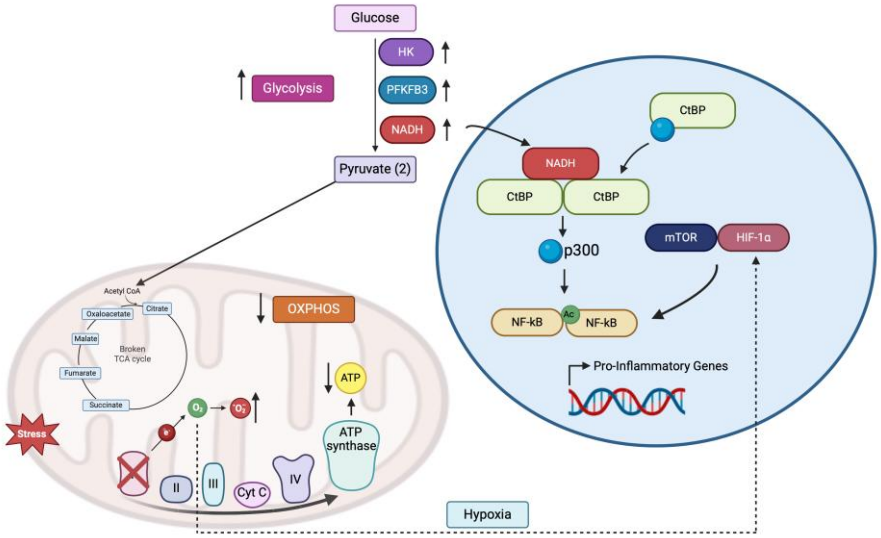

Figure 3: Excitotoxicity from exacerbated glutamate release leads to neuronal death. (A) The exacerbated release of glutamate (Glu) (blue circles) into the synaptic cleft by glutamatergic neurons generates an excitotoxic effect on motor neurons; the excitotoxic effect generates an influx of $Ca^{2+,}$ resulting in the opening of the NMDA receptor (1) and inhibition of GABAergic receptors. In the process, there is a deficit of the Mg^{2+} cation responsible for blocking the NMDA receptor, leading to neuronal death. **(B)** Astrocytes are the main recipients of residual glutamate from synapses; glutamate is then converted into glutamine by the enzyme glutamine synthetase (GS) and transported to the mitochondria. In the mitochondria, excess glutamine (Gln) is converted into Glu and ammonium (NH_4) by the enzyme phosphonoacetate gamma-aminotransferase (PAG). In the context of ALS, increased ammonia levels causes damage to the mitochondria with NH_4 leakage, inhibiting the Na^+K^+ATPase pump (2), resulting in an influx of sodium into the astrocyte, and by osmotic difference, water (H_2O) moves into the cell to dilute the sodium charges, generating edema and swelling processes in the tissue. **(C)** In ALS, there is a reduction in the concentration of ATP generated in the electron transport chain. In general, this is due to the loss of functionality of complex I, which has yet to be elucidated. The escape of electrons to oxygen leads to the synthesis of superoxide (ROS), causing mitochondrial damage and the loss of functionality of complex I.