neuroglia

MDPI

Review

The Double Face of Microglia in the Brain

Moisés Rubio-Osornio [1,†], Carmen Rubio [2,†], Maximiliano Ganado [3] and Héctor Romo-Parra [2,4,*]

[1] Neurochemistry Department, National Institute of Neurology and Neurosurgery MVS, Mexico City 14269, Mexico; moises.rubio@innn.edu.mx
[2] Neurophysiology Department, National Institute of Neurology and Neurosurgery MVS, Mexico City14269, Mexico
[3] Department of Bioterio, Xochimilco Campus, Metropolitan Autonomous University, Mexico City 04960, Mexico
[4] Psychology Department, Iberoamericana University, Mexico City 01376, Mexico
* Correspondence: p41366@correo.uia.mx
† These authors contributed equally to this work.

Abstract

The microglia, first identified by Pío del Río-Hortega, are resident macrophages in the CNS that aid in immune monitoring, synaptic remodeling, and tissue repair. Microglial biology's dual functions in maintaining homeostasis and contributing to neurodegeneration are examined in this review, with a focus on neurodegenerative disease treatment targets. Methods: We reviewed microglial research using single-cell transcriptomics, molecular genetics, and neuroimmunology to analyze heterogeneity and activation states beyond the M1/M2 paradigm. Results: Microglia maintains homeostasis through phagocytosis, trophic factor production, and synaptic pruning. They acquire activated morphologies in pathological conditions, releasing proinflammatory cytokines and reactive oxygen species via NF-κB, MAPK, and NLRP3 signaling. Single-cell investigations show TREM2 and APOE-expressing disease-associated microglia (DAM) in neurodegenerative lesions. Microglial senescence, mitochondrial failure, and chronic inflammation result from Nrf2/Keap1 redox pathway malfunction in ageing. Microglial interactions with astrocytes via IL-1α, TNF-α, and C1q result in neurotoxic or neuroprotective A2 astrocytes, demonstrating linked glial responses. Microglial inflammatory or reparative responses are influenced by epigenetic and metabolic reprogramming, such as regulation of PGC-1α, SIRT1, and glycolytic flux. Microglia are essential to neuroprotection and neurodegeneration. TREM2 agonists, NLRP3 inhibitors, and epigenetic modulators can treat chronic neuroinflammation and restore CNS homeostasis in neurodegenerative illnesses by targeting microglial signaling pathways.

Keywords: microglia; neuroinflammation; neurodegeneration; synaptic pruning; disease-associated microglia (DAM); TREM2; NLRP3; metabolic reprogramming; astrocytes; neuroglia

Academic Editor: Maximilian Wiesmann

Received: 31 October 2025
Revised: 2 December 2025
Accepted: 16 December 2025
Published: 2 January 2026

1. Introduction

Microglia, initially characterized by Pío del Río-Hortega in the early 20th century, are one of the most significant discoveries in cellular neurobiology [1]. Previously regarded solely as an immunological element of the central nervous system (CNS), microglia are increasingly acknowledged as multifunctional regulators that integrate immune surveillance, synaptic remodeling, and metabolic regulation. Originating from yolk sac progenitors of mesodermal lineage, they penetrate the embryonic neuroepithelium early in development, forming a self-renewing, long-lived population that endures throughout life [2,3]. In recent

decades, advancements in single-cell transcriptomics, high-resolution imaging, and molecular genetics have demonstrated that microglia are significantly more dynamic and diverse than previously believed [4]. They perpetually monitor the CNS microenvironment, preserving neuronal and synaptic homeostasis by phagocytosis, the production of neurotrophic substances, and reciprocal communication with neurons, astrocytes, and oligodendrocytes. In addition to immunological defense, microglia regulate processes like synaptic pruning, neurogenesis, apoptosis modulation, and redox equilibrium, establishing their crucial role in neural development and neurodegenerative disorders [5–8]. Under normal settings, microglia display a highly branched architecture, allowing them to sense tiny biochemical and electrical signals inside the brain parenchyma. In response to pathogenic or metabolic stress, they experience morphological and functional activation, assuming amoeboid traits and secreting cytokines, chemokines, and reactive oxygen species (ROS) [9]. This activation, previously classified under the basic M1/M2 framework, is now recognized as comprising a range of transcriptionally varied states, including the disease-associated microglia (DAM) found in Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis [10–12].

The adaptive capacity of microglia is significantly altered by metabolic reprogramming and epigenetic modulation [13]. The shifts between oxidative phosphorylation and glycolysis dictate their inflammatory or reparative characteristics, whilst chromatin remodeling, histone alterations, and DNA methylation shape their transcriptional identity in reaction to environmental stimuli [14]. This adaptability underpins the phenomenon of microglial priming seen in ageing, marked by chronic low-grade inflammation, mitochondrial dysfunction, and compromised antioxidant defenses, which heighten neuronal susceptibility to secondary insults. Microglia function within an extensive neuroglial network, maintaining ongoing communication with astrocytes and oligodendrocytes to regulate synaptic activity, energy consumption, and immunological status [15]. This intercellular communication, facilitated by contact-dependent chemicals, cytokines, and extracellular vesicles, delineates the advancement or resolution of neuroinflammatory responses. The identification of meningeal lymphatic vessels and their relationship with microglia has redefined the central nervous system as an immunologically active organ, establishing microglia as both metabolic sentinels and immune integrators [16]. Recent evidence indicates that disruptions in microglial metabolic and epigenetic control serve as convergent processes that connect oxidative stress, mitochondrial failure, and neuroinflammation in neurodegenerative disorders. We posited that microglial dysfunction resulting from disrupted redox balance, mitochondrial failure, and maladaptive metabolic or epigenetic reprogramming forms a key pathogenic axis that propels neurodegeneration [17,18]. The amalgamation of these molecular changes not only fosters chronic neuroinflammation but also impedes neuroglial communication and neuronal viability, indicating that treatment approaches aimed at microglial signaling and metabolism may reinstate CNS homeostasis. The objective of this review is to present a comprehensive and current synthesis of microglial biology, highlighting their morphological diversity, molecular signaling, and metabolic adaptability in both healthy and pathological contexts. This study examines the relationship between redox regulation, epigenetic control, and neuroglial interactions to clarify how microglia maintain CNS homeostasis and to discover possible therapeutic targets for neurodegenerative and neuroinflammatory diseases.

2. Microglia: "The Cells of Pío Del Río-Hortega"

Microglia, initially characterised by Pío del Río-Hortega in the early 20th century, are a distinct glial lineage of mesodermal origin, originating from yolk sac erythromyeloid progenitors that infiltrate the neuroepithelium during early embryonic development. In contrast to astrocytes and oligodendrocytes, which originate from neuroectoderm, microglia

constitute the resident immune population of the CNS, crucial for sustaining homeostasis, facilitating synaptic remodelling, and providing neuroprotection [19,20]. These cells are long-lived, self-renewing, and regionally heterogeneous across the CNS, reflecting local environmental cues and transcriptional programs.

Under healthy settings, microglia display a highly branched morphology with delicate motile processes that perpetually monitor the brain parenchyma. This continuous environmental monitoring enables them to detect ionic fluctuations, ATP gradients, and cytokine concentrations, preserving the intricate equilibrium between synaptic activity and immune surveillance [21,22]. Their dynamic processes establish transient contacts with neuronal somata, dendritic spines, and astrocytic endfeet, enabling microglia to function as sentries, sculptors, and caretakers of the neural network. Microglia release neurotrophic factors including BDNF, IGF-1, NGF, and TGF-β, which facilitate. They also phagocytose apoptotic neurones and eliminate superfluous or inactive synapses, especially during developmental stages and key periods of plasticity [23–25]. Microglia facilitate learning, memory consolidation, and circuit maturation through synaptic refinement. They additionally engage in apoptotic control by releasing signals such as phosphatidylserine-binding receptors (MerTK, Axl) and complement system components (C1q, C3), facilitating the selective removal of cellular debris without inducing inflammation (Figure 1).

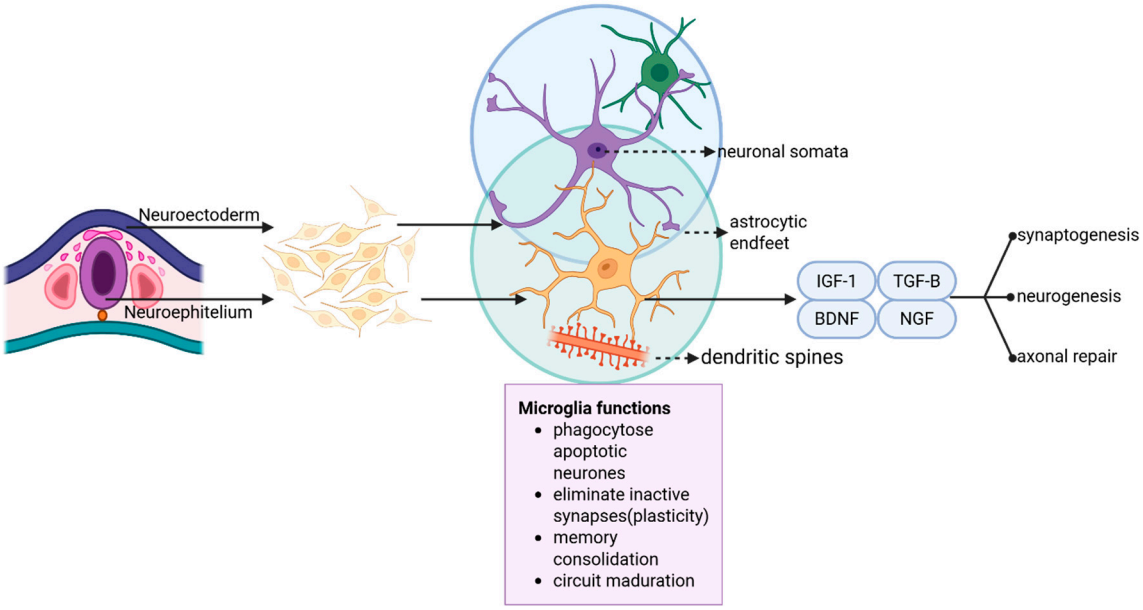

Figure 1. Central nervous system microglia origin, migration, and neurotrophic functions. Microglia, first identified by Pío del Río-Hortega, start as yolk sac erythro-myeloid progenitors that permeate the neuroepithelium during early development, producing the CNS immune cell population. Microglia become highly branched and constantly monitor the brain parenchyma via motile processes that engage neurones, synapses, and astrocytic endfeet. Normal microglia maintain CNS homeostasis by phagocytosing apoptotic neurones, eliminating inactive or redundant synapses to improve synaptic plasticity, and promoting learning, memory consolidation, and neural circuit remodelling. The release of neurotrophic and growth factors, such as BDNF, IGF-1, NGF, and TGF-β, aids neuronal survival, differentiation, and synaptic refinement. Microglia maintain the delicate balance between immune monitoring and neuroplasticity as neural network sentinels, sculptors, and caretakers.

Table 1 shows the transcriptomic categorization of microglial subgroups in both health and neurodegenerative disorders. This table delineates the principal microglial subtypes found via single-cell RNA sequencing, emphasizing their essential molecular markers, fundamental functions, and relevant clinical settings. The classification illustrates the dynamic and context-sensitive characteristics of microglial activation, transcending the

conventional M1/M2 framework to a more nuanced and functionally varied spectrum pertinent to neurodegenerative diseases.

Table 1. Microglial Subtypes Identified by Single-Cell Transcriptomics.

Microglia Subtype	Key Molecular Features	Main Functions	Associated Conditions	References
Homeostatic Microglia	Tmem119, P2ry12, Cx3cr1, Sall1	Synaptic homeostasis, immune surveillance	Healthy brain, early aging	[26,27]
Disease-Associated Microglia	Apoe, Lpl, Cst7, Trem2, Tyrobp	Phagocytosis, debris clearance, response to misfolded proteins	Alzheimer's, Parkinson's, ALS	[28]
Interferon-Responsive Microglia	Ifit2, Ifit3, Irf7, Isg15	Antiviral response, interferon-driven inflammation	Alzheimer's, viral infections, chronic neuroinflammation	[20]
Pro-inflammatory Microglia	Il1b, TNF, Ccl2, Nos2	Cytokine production, amplification of neuroinflammation	Demyelinating diseases, acute injury, neurotoxicity	[29,30]
Aging-Related Microglia	Gpnmb, Dap12, Lgals3, Cd9	Cellular stress response, senescence-associated dysfunction	Aging, late-stage Alzheimer's	[26]
Proliferative Region-Associated Microglia	Mki67, Top2a, Cdk1	Tissue repair, local clonal expansion	Active neurodegeneration, traumatic injury	[20]
Transitional Microglia	Mixed signatures: P2ry12, Apoe, Lpl	Intermediate state between homeostatic and DAM	Early-stage Alzheimer's, neurodegeneration	[31,32]
Myelin-Associated Microglia	Spp1, Itgax, Lpl	Myelin phagocytosis, axonal repair	Multiple sclerosis, toxic demyelination	[20]
Neuroprotective Microglia	Igf1, Apoe, Spp1	Neuronal survival promotion, trophic support	Acute injury, early neurodegeneration	[33]

3. Microglial Activation and Functional Polarization

Under pathological or stressful stimuli such as tissue injury, infection, trauma, or metabolic imbalance microglia undergo profound morphological and functional transformations, retracting their processes and acquiring an amoeboid shape characteristic of phagocytic activation. This transition is accompanied by the upregulation of pattern-recognition receptors (PRRs) such as TLR4, NOD2, and TREM2, which activate intracellular signaling cascades including NF-κB, MAPK, and JAK/STAT, culminating in the release of proinflammatory cytokines (IL-1β, TNF-α, IL-6), chemokines, and reactive oxygen and nitrogen species (ROS/RNS) [34–40]. Historically, microglial activation was simplified into two phenotypes, M1 (proinflammatory, cytotoxic) and M2 (anti-inflammatory, reparative). Single-cell transcriptomics has revolutionised our understanding of microglial diversity, showing that these cells have a continuum of context-dependent transcriptional states in health and disease [26]. Large-scale single-cell RNA-sequencing has identified multiple microglial subsets, including homeostatic, disease-associated, interferon-responsive, and proliferative or transitional phenotypes, each with distinct molecular signatures and functional roles [31]. This improved classification has illuminated how microglia dynamically respond to neurodegeneration, inflammation, and metabolic stress, providing a more pre-

cise framework for understanding microglial activation across neurological illnesses [20]. Thus, this new perspective is essential for understanding microglial states' complicated role in neurodegenerative disease pathogenesis [41].

However, advances in single-cell RNA sequencing have revealed a much more complex transcriptional continuum, with diverse and context-dependent states that cannot be captured by a binary model [12,42–44]. Among these, disease-associated microglia (DAM) and neurodegeneration-associated microglia (NAM) have been characterized by the expression of TREM2, APOE, CST7, LPL, and TYROBP, particularly within amyloid-rich or degenerating brain regions such as those seen in Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [12,31,45–47] (Figure 2).

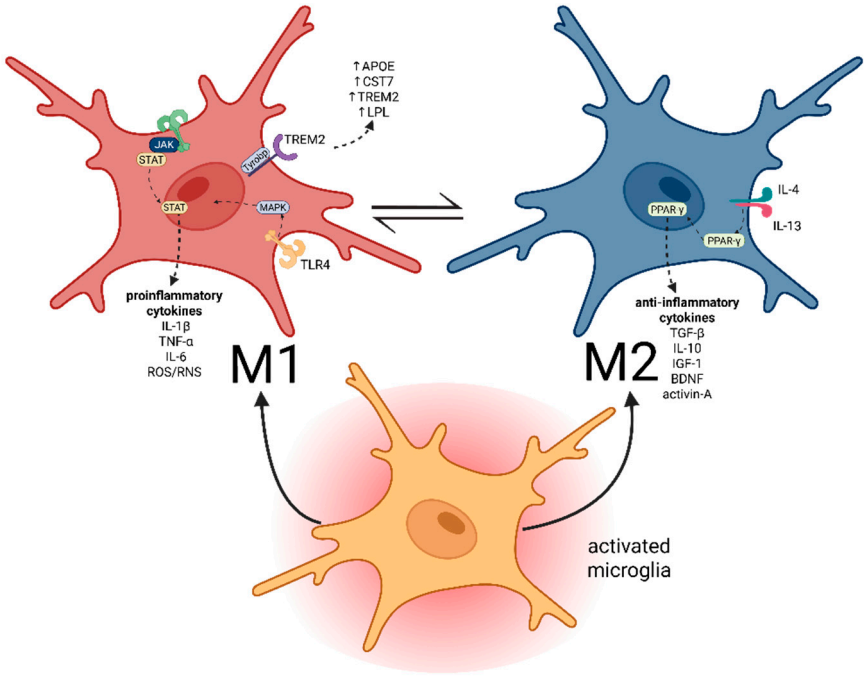

Figure 2. Central Nervous System Microglial Polarisation and Activation. The figure shows how intracellular signalling pathways polarise microglia into pro-inflammatory (M1) and anti-inflammatory/reparative (M2) functional phenotypes. Classically activated microglia, the M1 Polarisation (Red Cell), activates the JAK-STAT and MAPK signalling pathways. Signalling by surface receptors such Tyrobp increases pro-inflammatory gene transcription, causing neuroinflammation and neurotoxicity. M2 Polarisation (Blue Cell) signals alternatively activated microglia that heal tissue and reduce inflammation. This phenotype involves activation of the nuclear receptor PPAR-γ, which promotes anti-inflammatory and neuroprotective gene expression by nuclear translocation. The yellow microglial cell with a crimson halo in the lower image shows morphological activity in inflammation. The hypertrophic soma and retraction of ramified processes indicate activation and migration to the injury site (partial labels "act" and "mi" suggest "activation" and "migration" or "microenvironment"). The graphic shows how intracellular signalling pathways determine the microglial phenotype, which is critical to neurodegenerative disease development and treatment.

4. Neuroimmune Integration and Microglial Modulation: Therapeutic Strategies

Through targeted microglial activity modulation and tissue homeostasis restoration, neuroimmune integration is crucial to understanding and treating neurodegenerative disorders [41]. In models of Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis, shifting microglia from the pro-inflammatory M1 phenotype to the reparative M2 state reduces chronic neuroinflammation and promotes neuroprotection [41]. Within this therapeutic framework, growing attention has focused on bioactive natural substances,

nutraceuticals, and phytochemicals capable of inducing M2 polarization and modulating key microglial metabolic pathways, including oxidative metabolism, mitochondrial biogenesis, and Nrf2-driven antioxidant signaling [48]. Curcumin, resveratrol, quercetin, and omega-3 fatty acids inhibit pro-inflammatory cytokine production and alter microglial metabolism to increase oxidative phosphorylation [49–52]. Effects of Resveratrol, Curcumin and Quercetin Supplementation on Bone Metabolism and Curcumin and resveratrol administration in Alzheimer's models results in reduced amyloid load, microglial activation, and improved hippocampal-dependent learning and memory [53]. It suggests that substances like epigallocatechin-3-gallate and polyphenols from Ginkgo biloba can reduce microglial activation and boost dopaminergic neurone survival in Parkinson's disease by inhibiting NF-κB and activating AMPK [54,55]. Omega-3 fatty acids and alpha-lipoic acid reduce reactive oxygen species, increase glutathione, and modulate microglial energy metabolism in ALS models [56,57]. Even more that therapeutic modulation of the neuroimmune interface using nutraceuticals and phytochemicals can improve microglial balance, neurorepair, and slow the progression of neurodegenerative diseases with persistent inflammation [58].

5. Microglia Metabolic Modulation by Bioactive Natural Compounds

The increasing interest in natural immunomodulators as regulators of microglial phenotype has resulted in a burgeoning body of evidence indicating that bioactive substances, nutraceuticals, and phytochemicals can efficiently induce microglial M2 polarization by modulating cellular metabolism. Microglial phenotypic changes are meticulously regulated by metabolic conditions, pro-inflammatory M1 activation primarily depends on glycolysis, while the neuroprotective M2 phenotype relies on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO). Numerous natural substances have demonstrated a direct impact on these metabolic pathways. Curcumin induces an AMPK-dependent metabolic shift that diminishes glycolytic activity while augmenting mitochondrial respiration, thus promoting a change to an M2-like phenotype marked by elevated Arg1 and IL-10 expression [14,59]. Resveratrol has been documented to activate the SIRT1/PGC-1α axis, enhancing mitochondrial biogenesis and restoring redox equilibrium, which together mitigate LPS-induced M1 activation and promote an anti-inflammatory microglial state [60,61]. Flavonoids like quercetin and luteolin have synergistic effects by regulating essential transcriptional pathways, specifically NF-κB and Nrf2; NF-κB inhibition reduces pro-inflammatory gene expression, whereas Nrf2 activation boosts antioxidant defences and facilitates the metabolic requirements of M2 polarization [62]. Recent studies emphasize the significance of terpenoids and polyphenols in modulating microglial lipid metabolism, an essential regulator of immune cell function. These chemicals enhance fatty acid oxidation and lipid droplet mobilization, both crucial for sustaining the anabolic and reparative processes linked to M2 microglia [63]. Collectively, our data indicates that natural substances not only reduce inflammation but also directly influence microglial metabolic programming, redirecting bioenergetic pathways to facilitate tissue repair, phagocytic clearance, and neuroprotection. Integrating these findings into the study highlights the therapeutic potential of natural immunomodulators as agents for metabolic reprogramming that can promote advantageous microglial states in neurodegenerative disorders.

6. Aging, Metabolism, and Oxidative Vulnerability

Microglia have metabolic adaptability, oxidative phosphorylation (OXPHOS), facilitates homeostatic tasks, whereas a transition to glycolysis promotes proinflammatory activity via HIF-1α stabilization and mTOR signaling activation. In contrast, the activation of PGC-1α, SIRT1, and AMPK enhances mitochondrial biogenesis and antioxidative pathways, reinstating a reparative phenotype [18,64–66]. With ageing, microglia collect

lipofuscin, lysosomal debris, and iron, demonstrating less phagocytic efficacy and a persistent proinflammatory state an altered situation referred to as microglial priming [67–70]. This persistent activation increases neuronal vulnerability to future damage and is linked to mitochondrial dysfunction, disrupted Nrf2/Keap1 redox signaling, and modified metabolic flexibility [71–75]. Senescent microglia exhibit reduced antioxidant capabilities, heightened reactive oxygen species production, and impaired mitophagy, all contributing to oxidative stress and synaptic injury [76,77] (Figure 3).

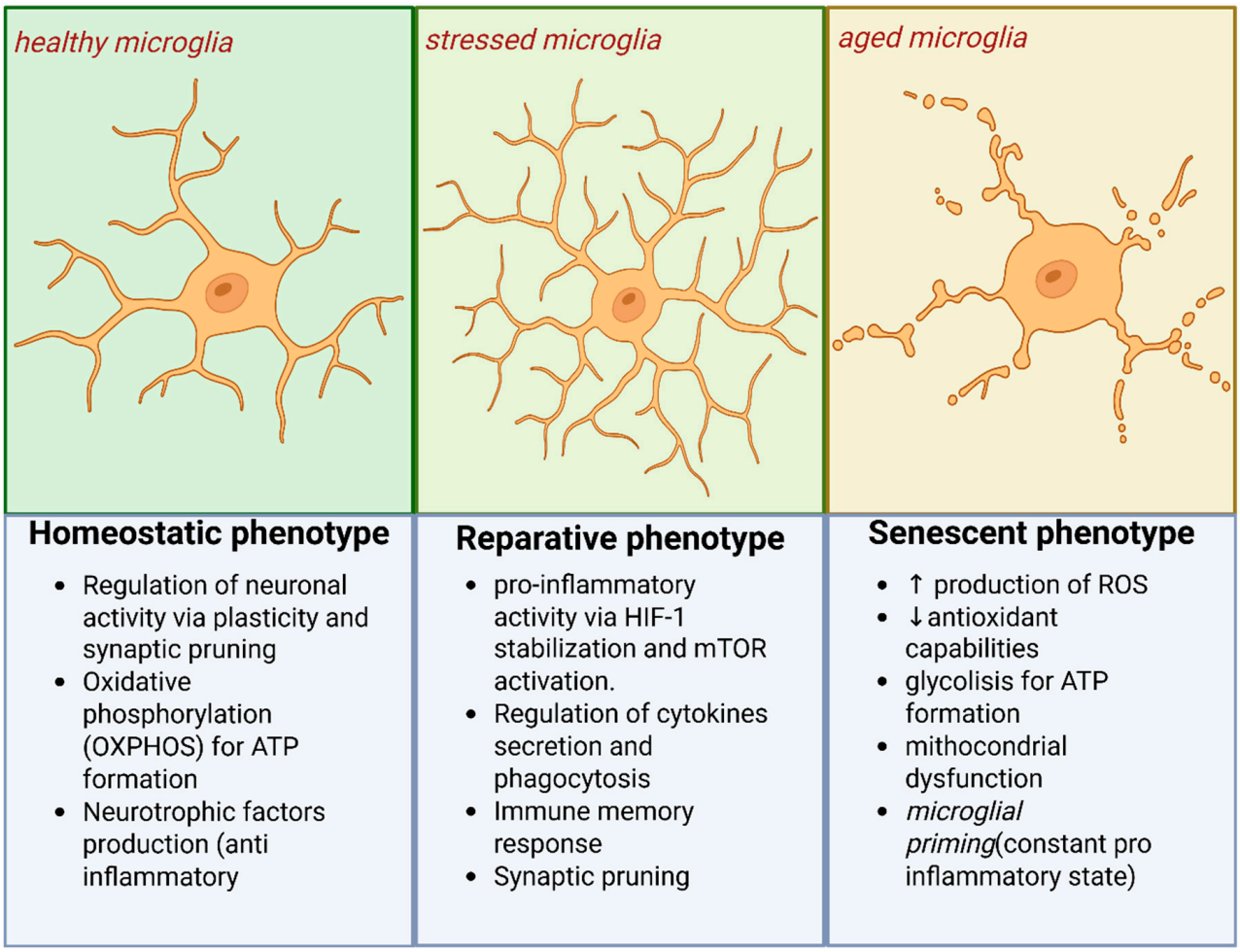

Figure 3. Physiological, stress-related, and ageing microglial phenotypes. In response to cellular stress and ageing, microglia adjust metabolically and functionally. Homeostatic microglia use oxidative phosphorylation (OXPHOS) to stimulate neuronal activity, synaptic pruning, and neurotrophic and anti-inflammatory release. Stress triggers a metabolic shift to glycolysis, involving HIF-1α stabilisation and mTOR activation, leading to cytokine release, phagocytic activity, and immunological memory responses. Microglia accumulate lipofuscin, iron, and lysosomal debris as people age, causing mitochondrial dysfunction, antioxidant capacity loss, ROS production, and microglial priming. This ageing phenotype causes neuroinflammation, oxidative stress, and neuronal vulnerability.

7. Epigenetic and Transcriptional Control of Microglial Identity

The transcriptional identity of microglia is meticulously governed by epigenetic mechanisms, encompassing DNA methylation, histone acetylation (H3K27ac), and chromatin remodeling facilitated by enzymes such as TET2, HDACs, and SWI/SNF complexes [78,79]. These alterations enable microglia to retain recollections of previous inflammatory occurrences, a phenomenon known as trained immunity or innate immunological memory [18]. Epigenetic reprogramming facilitates the persistence of inflammatory markers evident

in ageing, neurodegeneration, and metabolic diseases. Microglial diversity is also influenced by region-specific transcription factors, including Sall1, IRF8, PU.1, and Cx3cr1, which integrate developmental and environmental inputs to sustain the homeostatic phenotype. Interruption of these systems results in maladaptive activation and a decline in neuroprotective capabilities [80,81] (Figure 4).

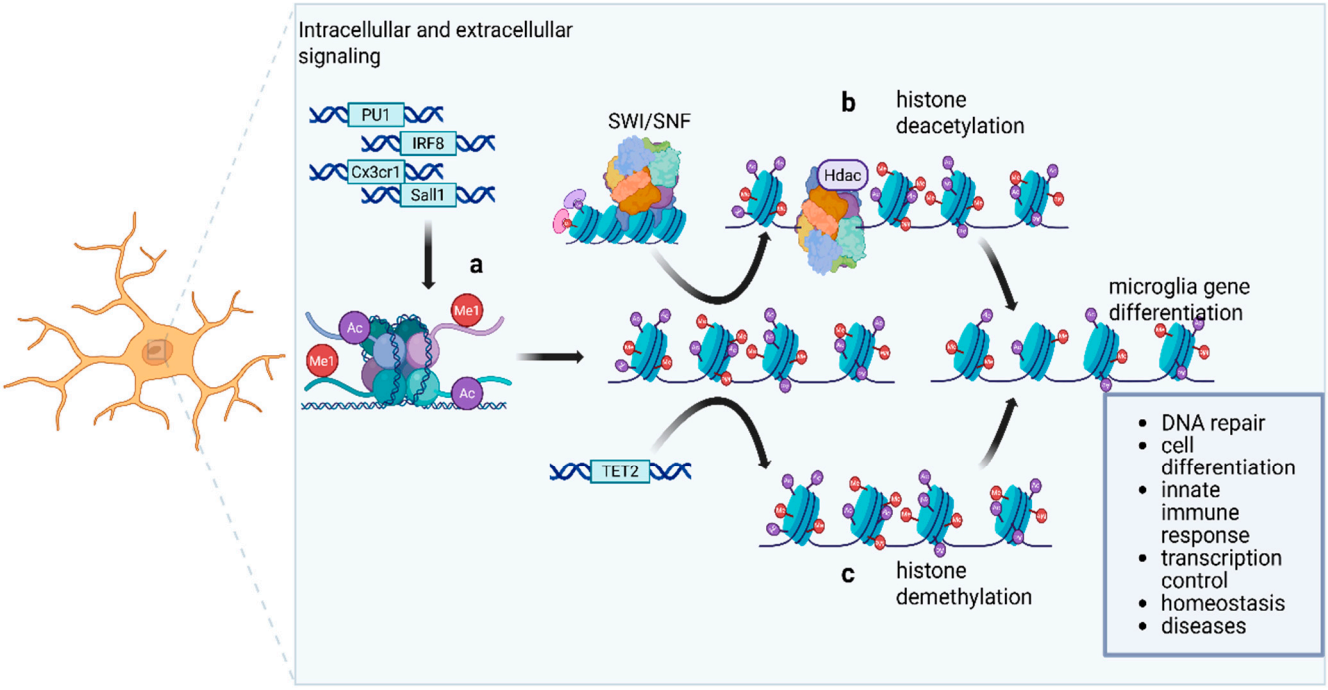

Figure 4. Microglial Genetic Differentiation Epigenetic Regulation. The figure shows the chemical signalling cascade and epigenetic processes that regulate microglial gene differentiation and activity. Essential transcription factors including PU1, IRF8, Cx3cr1, and Sall1 are controlled by intracellular and extracellular signalling. Initial Repression and Remodelling. These elements use a chromatin remodelling complex, possibly the SWI/SNF complex, to condense chromatin. In restrictive environments, nucleosomes undergo methylation (Me1) and acetylation (Ac). (**b**) Histone Deacetylation: Hdac removes acetyl groups from histones, causing chromatin condensation and gene regulation. (**c**) Histone Demethylation: TET2 (Ten-Eleven Translocation 2) demethylates DNA or histones, which is necessary for state alteration along with chromatin remodelling. Chromatin remodelling, including deacetylation and demethylation, helps microglia genetically differentiate, affecting DNA repair, cell differentiation, innate immune response, transcription regulation, homeostasis, and disease susceptibility. The magnified box illustrates the mechanism of epigenetic regulation in microglia (a glial cell), where intracellular and extracellular signaling activates transcription factors (PU.1, IRF8, Sall1) that bind to DNA to initiate chromatin remodeling and histone modifications (acetylation and methylation), a fundamental step that determines the genetic differentiation and functional state of this central nervous system immune cell.

8. Microglia and Neuroglial Communication

Contemporary neuroscience has redefined the central nervous system as a neuroglial network, in which microglia, astrocytes, and oligodendrocytes operate as coordinated regulators of synaptic, metabolic, and immunological balance. Microglial-neuronal interactions occur through contact-dependent molecules such CX3CL1-CX3CR1 and CD200-CD200R, as well as soluble mediators like ATP, cytokines, nitric oxide, and extracellular vesicles [82–85]. These connections align brain activity with local immunological and metabolic states. Astrocytes, hitherto regarded just as supportive cells, undergo functional change in conjunction with microglia. Activated microglia release IL-1α, TNF-α, and C1q, which promote the

generation of A1 neurotoxic astrocytes, whereas anti-inflammatory microglia support the production of A2 neuroprotective astrocytes. This bidirectional communication determines the termination of the inflammatory response or its progression towards chronic neurodegeneration [86–90]. Furthermore, microglia influence the maturation of oligodendrocyte progenitors and the turnover of myelin through the secretion of factors such as IGF-1 and PDGF, underscoring their significant role in maintaining white matter integrity [91–94] (Figure 5).

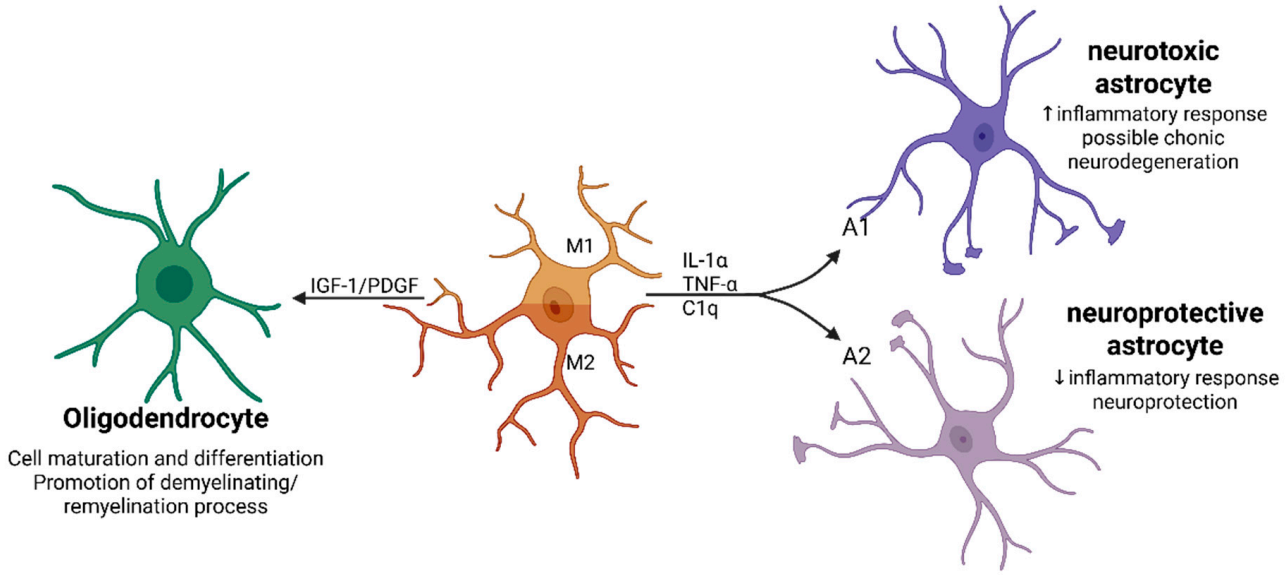

Figure 5. Microglial or Neuronal Cell Morphological Progression Schematic. The image shows cell morphological changes caused by central nervous system activation, differentiation, or stimulation. A basal or resting cell with a spherical soma and delicate, homogenous dendritic processes or extensions is the Initial Cell (Green). In microglia, this means ramified or surveillance morphology. Intermediate Cell (Orange/Red) has a considerably bigger soma and thicker, retracted processes. This signifies cell activity or reactive state, preparing for migration or phagocytosis. end Cells (Purple/Lilac): Show two possible outcomes. The cells' somas are larger and their operations are simpler. This could mean: Amoeba morphology. Complete activation (dark purple) relates to phagocytosis and acute inflammation (microglia). Senescent or Dystrophicmorphology: A modified state (lilac) with reduced cellular reactivity and fragmented processes, often seen in ageing or chronic disorders. The image shows cellular plasticity in response to microenvironmental changes, a key concept in neuroscience and CNS immunology.

9. Microglia in Development, Synaptic Plasticity, and Apoptosis

In addition to participating in immune surveillance, microglia facilitate brain growth. Amoeboid microglia regulate neuronal death, phagocytose apoptotic bodies, and produce trophic factors that affect neural patterning during embryogenesis. Microglia are responsible for the refinement of synaptic connections in the postnatal brain. This is accomplished through complement-mediated pruning and activity-dependent engulfment of fragile synapses [95–98].

Microglia are responsible for maintaining synaptic homeostasis in the mature brain. They accomplish this by monitoring neuronal firing rates and adjusting neurotransmitter availability. Microglia can selectively detect ATP generated by activated synapses via P2Y12 receptor signaling. This allows them to concentrate their efforts on areas of significant activity, therefore stabilising or reorganising the current connections. The dynamics of microglia are linked to the mechanisms of learning and memory because of this ability [99–102], as shown in Figure 6.

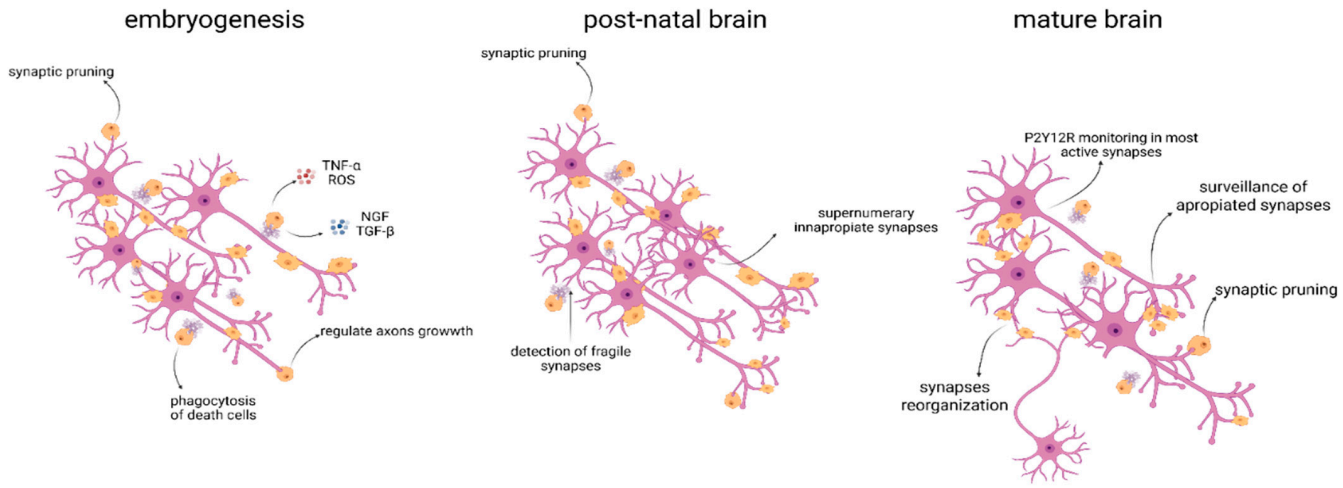

Figure 6. Complex Cellular Network Structure and Interactions. Three panels demonstrate the design and complexity of a cellular network, either neurones or heavily branching glial cells like microglia or astrocytes in the central nervous system. The little yellow/orange structures along the cellular processes may be synaptic connections or pathogenic deposits like plaques. (**Left panel**). This dense, interwoven network has various yellow structures. The network's red and blue squares may indicate markers or sites of interest, e.g., inflammation, damage, or protein expression. The (**Middle Panel**) has a similarly branched network with a constant yellow component distribution, suggesting greater complexity or synaptic density than the left panel. In the (**right panel**), certain processes look thicker or retracted, and branching may be reduced in some regions, indicating remodelling or response to a stimulus. The panels compare multiple phases of cellular connection and morphological complexity needed to understand brain neuronal plasticity, synaptic function, and neuroinflammatory reactions.

10. Microglia, Redox Homeostasis, and Mitochondrial Communication

Microglia are both producers and sensors of oxidative stress. Under inflammatory conditions, excessive ROS/RNS generation through NADPH oxidase (NOX2), and inducible nitric oxide synthase (iNOS), leads to mitochondrial impairment and bioenergetic crisis [103–106]. Mitochondrial dysfunction, in turn, releases mitochondrial DNA and cardiolipin, acting as damage-associated molecular patterns (DAMPs), that perpetuate inflammation via NLRP3 inflammasome activation [107–111]. Conversely, microglia can adopt an antioxidant phenotype by upregulating Nrf2-dependent transcription and enhancing glutathione (GSH) metabolism. The interplay between redox balance, mitochondrial health, and inflammatory tone positions microglia as central hubs of CNS metabolic regulation [41,112], as shown in Figure 7.

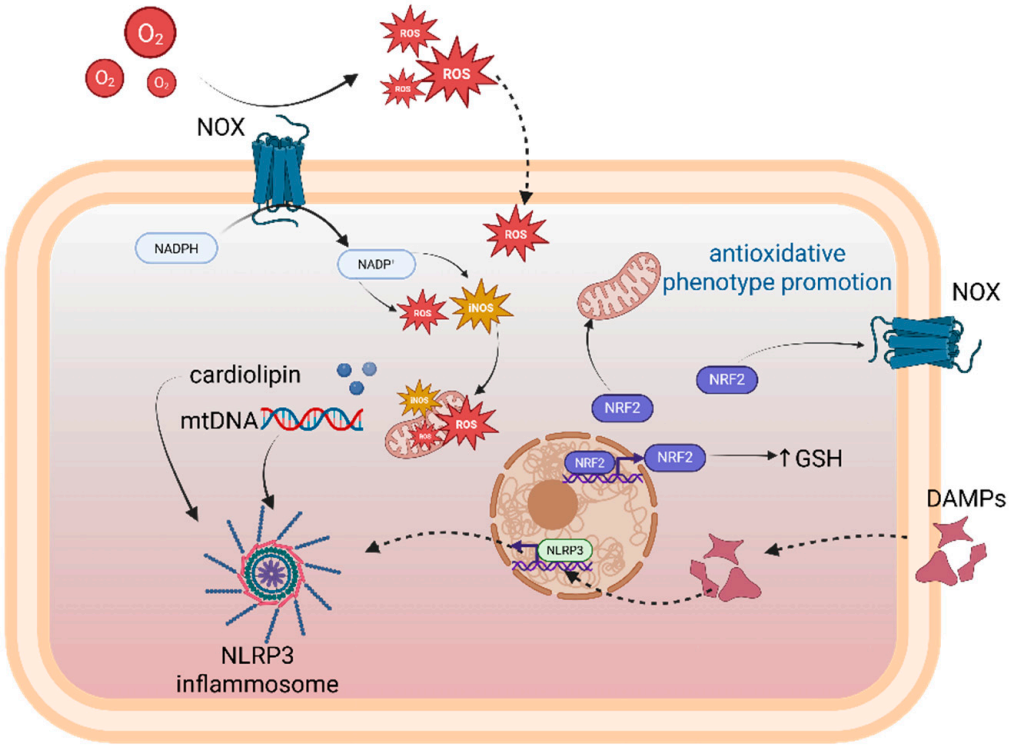

Figure 7. Oxidative Stress, Mitochondrial Injury, and NLRP3 Inflammasome Activation. ROS generation activates defensive antioxidant responses and the pro-inflammatory NLRP3 inflammasome, as seen in the graphic. The process starts with ROS generation from NADPH oxidase and exogenous ROS influx. As signalling molecules, reactive oxygen species have two main impacts. ROS initially activate NRF2. NRF2 translocates to the nucleus, interacts with DNA, and upregulates antioxidant genes, increasing GSH and promoting an antioxidative phenotype. Second, excessive ROS generation damages mitochondria and releases DAMPs into the cytosol. DAMPs include cardiolipin and mitochondrial DNA. These DAMPs activate the NLRP3 inflammasome complex, a key component of the innate immune response, causing inflammation and cellular death as shown by cellular constituent release. This figure shows the delicate balance between the NRF2-mediated protective mechanism and the NLRP3-mediated inflammatory response to oxidative stress and mitochondrial dysfunction. Intercellular signalling networks define the microglial phenotype, which is crucial to neurodegenerative disease aetiology and treatment.

11. Neuroimmune Integration and Therapeutic Perspectives

The identification of meningeal lymphatic vessels and their relationship with microglia has redefined the CNS as an immunologically active organ. This paradigm change has introduced novel treatment techniques aimed at microglial signalling and metabolism. The modulation of microglial activity with TREM2 agonists, NLRP3 inhibitors, CSF1R blockers, or epigenetic modulators (HDAC and BET inhibitors), has potential to restore homeostasis, mitigate chronic inflammation, and enhance neurorepair in conditions such as Alzheimer's, Parkinson's, and ALS [113–116]. Microglia are now recognized not just as immunological sentinels but also as integrative regulators that connect immune defense, synaptic plasticity, metabolism, and tissue remodeling. The structural and functional plasticity, as conceptualized by Río-Hortega over a century ago, continues (Figure 8).

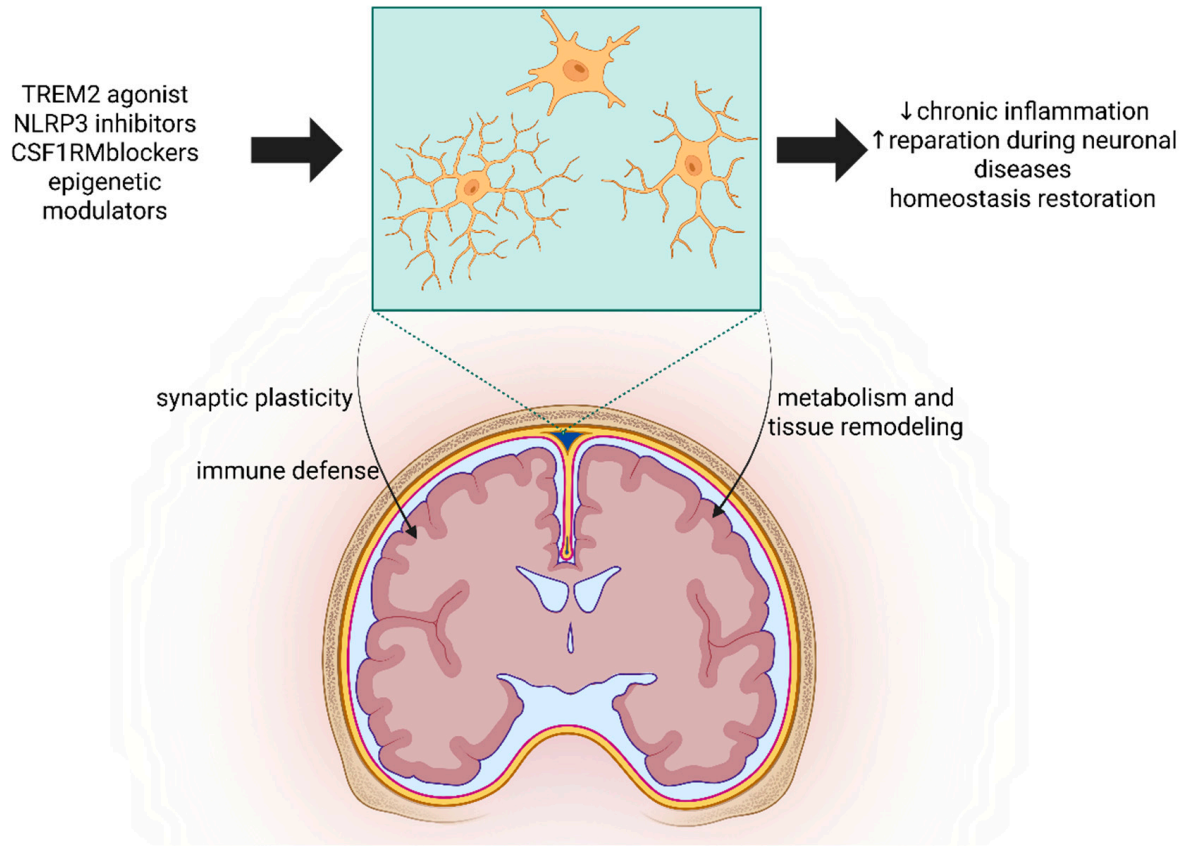

Figure 8. Complex Functions of Microglia in Cerebral Homeostasis and Operation. Microglial cells regulate many aspects of central nervous system (CNS) health and illness, as shown in this brain cross-section. The inset highlights resting or scanning microglia's ramified architecture, which constantly monitors the brain. Brain cells perform crucial roles, as seen by the arrows. Microglia, the main immune cells in the CNS, play a significant role in synaptic plasticity through synaptic pruning and immunological defence. On the right, they help remove cellular trash and repair neural tissue through metabolism and tissue remodelling. The graphic shows that microglial function goes beyond immune surveillance to protect the brain's function and structure.

12. Insights from Microglia Knockout Models in Neurodegeneration

Mouse models with microglia depletion have proven crucial for elucidating the precise role of microglial cells in the initiation and advancement of neurodegenerative disorders, including amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) and Alzheimer's disease (AD). Research on ALS/FTD indicates that conditional microglial deletion via Cx3cr1-Cre-driven diphtheria toxin receptor (DTR) systems or CSF1R inhibitors diminishes inflammatory signalling, alters disease progression, and partially enhances motor neurone survival in models with C9orf72 repeat expansions or TREM2 mutations. This suggests that microglia play an active role in shaping the neurodegenerative environment rather than simply reacting to neuronal damage [117,118]. Further investigations in SOD1G93A ALS models revealed that inducible microglia depletion during symptomatic stages results in decreased levels of TNF-α, IL-1β, and oxidative stress markers, as well as a slight increase in survival, underscoring the detrimental role of persistent microglial activation in worsening mitochondrial dysfunction and excitotoxicity [119,120]. Notably, the ablation of microglia during presymptomatic phases did not prevent the onset of illness, suggesting that the role of microglia may be stage-dependent and interconnected with first neuronal-autonomous processes [121,122]. In FTD models with GRN deficiency, the selective ablation of microglia worsens synaptic loss and hastens neurodegeneration, rein-

forcing the notion that microglia may have neuroprotective functions influenced by context, genetic background, and timing [123]. Microglia-depletion models have been essential in clarifying the dual involvement of microglia in amyloid and tau pathology within the context of Alzheimer's disease. Research utilising CSF1R inhibitors like PLX3397 or genetic DTR-mediated ablation demonstrated that the elimination of microglia during the initial amyloidogenic phases diminishes neuritic dystrophy and attenuates proinflammatory cytokine production; however, it also compromises the microglial barrier typically established around accumulating Aβ plaques, consequently enhancing plaque dispersion and cortical pathology [124–126]. In contrast, the depletion of microglia during advanced illness stages intensifies tau dissemination and synaptic disconnection, indicating that microglia serve as essential regulators of tau propagation, debris clearance, and the preservation of synaptic homeostasis as the pathology advances [127,128]. Models featuring TREM2 knockout or loss-of-function variants underscore that compromised microglial responses disrupt lipid metabolism, phagocytosis, and plaque compaction, resulting in more diffuse amyloid deposits and expedited cognitive decline. This illustrates that microglial reactivity is not uniformly harmful but is instead highly contingent upon the microglial phenotypic state and disease phase [121,129,130]. Collectively, evidence from microglia-depletion mouse models in ALS/FTD and Alzheimer's disease robustly substantiates the concept that microglia function as dynamic modulators of neuroinflammation, synaptic integrity, metabolic homeostasis, and the propagation of pathogenic proteins. These models offer essential mechanistic understanding of the timing and way in which microglia contribute to neurodegeneration, highlighting the therapeutic significance of precisely manipulating microglial activity [131,132].

13. Conclusions

Microglia, previously considered passive immune sentinels, have been recognized as dynamic and multifunctional regulators of central nervous system (CNS) integrity. They regulate synaptic pruning, metabolic coordination, and neuroimmune monitoring from development to ageing through precisely controlled molecular networks. Their capacity to transition between protective and harmful states relies on precisely regulated systems related to redox homeostasis, mitochondrial integrity, and epigenetic modification. Disruptions in these regulatory pathways, specifically mitochondrial malfunction, oxidative stress, and abnormal inflammatory signalling, convert microglia from neuroprotective allies into instigators of chronic neuroinflammation and neuronal degeneration. Integrating findings from transcriptomics, metabolism, and neuroimmunology reveals that microglia function as both sensors and effectors of CNS homeostasis, making them critical therapeutic targets for the prevention and treatment of neurodegenerative disorders.

14. Perspectives

Future investigations should focus on elucidating the temporal and regional variability of microglial phenotypes by integrative single-cell and spatial omics methodologies. Comprehending the influence of metabolic reprogramming, mitochondrial communication, and epigenetic memory on microglial responses is key for developing therapies that restore physiological equilibrium while preserving vital immunological and trophic activities. Therapeutic regulation of critical pathways such as TREM2, NLRP3, and Nrf2/Keap1 is a promising strategy to mitigate chronic neuroinflammation and facilitate regeneration. Moreover, investigating the interactions between microglia and astrocytes, as well as between microglia and neurons, may uncover novel molecular checkpoints for regulating neurotoxic cascades and improving synaptic resilience. Ultimately, integrating these discoveries into targeted therapeutics could transform our ability to maintain cognitive function

and decelerate the advancement of neurodegenerative illnesses by reinstating the delicate balance that Río-Hortega initially conceptualized at the inception of microglial biology.

Author Contributions: Conceptualization, M.R.-O. and C.R.; writing—original draft preparation, M.R.-O. and C.R.; writing—review and editing, H.R.-P.; supervision, H.R.-P.; project administration, H.R.-P.; visualization, M.G. All authors have read and agreed to the published version of the manuscript.

Funding: The authors declare that there are no funds to disclose and gratefully acknowledge the Instituto Nacional de Neurologíay Neurocirugía for its support.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare that there is no conflict of interest.

References

1. Boullerne, A.I.; Feinstein, D.L. History of Neuroscience I. Pío del Río-Hortega (1882–1945): The Discoverer of Microglia and Oligodendroglia. *ASN Neuro* **2020**, *12*, 1759091420953259. [CrossRef] [PubMed]
2. Schafer, D.P.; Stevens, B. Microglia Function in Central Nervous System Development and Plasticity. *Cold Spring Harb. Perspect. Biol.* **2015**, *7*, a020545. [CrossRef]
3. Holloway, R.K.; Zhang, L.; Molina-Gonzalez, I.; Ton, K.; Nicoll, J.A.R.; Boardman, J.P.; Liang, Y.; Williams, A.; Miron, V.E. Localized microglia dysregulation impairs central nervous system myelination in development. *Acta Neuropathol. Commun.* **2023**, *11*, 49. [CrossRef]
4. Lyu, J.; Jiang, X.; Leak, R.K.; Shi, Y.; Hu, X.; Chen, J. Microglial Responses to Brain Injury and Disease: Functional Diversity and New Opportunities. *Transl. Stroke Res.* **2021**, *12*, 474–495. [CrossRef]
5. Shi, Q.; Gutierrez, R.A.; Bhat, M.A. Microglia, Trem2, and Neurodegeneration. *Neuroscientist* **2025**, *31*, 159–176. [CrossRef] [PubMed]
6. Marín-Teva, J.L.; Sepúlveda, M.R.; Neubrand, V.E.; Cuadros, M.A. Microglial Phagocytosis During Embryonic and Postnatal Development. *Adv. Neurobiol.* **2024**, *37*, 151–161.
7. Navabi, S.P.; Badreh, F.; Khombi Shooshtari, M.; Hajipour, S.; Moradi Vastegani, S.; Khoshnam, S.E. Microglia-induced neuroinflammation in hippocampal neurogenesis following traumatic brain injury. *Heliyon* **2024**, *10*, e35869. [CrossRef] [PubMed]
8. Wiens, K.R.; Wasti, N.; Ulloa, O.O.; Klegeris, A. Diversity of Microglia-Derived Molecules with Neurotrophic Properties That Support Neurons in the Central Nervous System and Other Tissues. *Molecules* **2024**, *29*, 5525. [CrossRef]
9. Wu, Q.; Zou, C. Microglial Dysfunction in Neurodegenerative Diseases via RIPK1 and ROS. *Antioxidants* **2022**, *11*, 2201. [CrossRef]
10. Devanney, N.A.; Stewart, A.N.; Gensel, J.C. Microglia and macrophage metabolism in CNS injury and disease: The role of immunometabolism in neurodegeneration and neurotrauma. *Exp. Neurol.* **2020**, *329*, 113310. [CrossRef]
11. Shan, M.; Lin, S.; Li, S.; Du, Y.; Zhao, H.; Hong, H.; Yang, M.; Yang, X.; Wu, Y.; Ren, L.; et al. TIR-Domain-Containing Adapter-Inducing Interferon-β (TRIF) Is Essential for MPTP-Induced Dopaminergic Neuroprotection via Microglial Cell M1/M2 Modulation. *Front. Cell Neurosci.* **2017**, *11*, 35. [CrossRef]
12. Guo, S.; Wang, H.; Yin, Y. Microglia Polarization from M1 to M2 in Neurodegenerative Diseases. *Front. Aging Neurosci.* **2022**, *14*, 815347. [CrossRef] [PubMed]
13. Shaik, S.M.; Cao, Y.; Gogola, J.V.; Dodiya, H.B.; Zhang, X.; Boutej, H.; Han, W.; Kriz, J.; Sisodia, S.S. Translational profiling identifies sex-specific metabolic and epigenetic reprogramming of cortical microglia/macrophages in APPPS1-21 mice with an antibiotic-perturbed-microbiome. *Mol. Neurodegener.* **2023**, *18*, 95. [CrossRef]
14. Orihuela, R.; McPherson, C.A.; Harry, G.J. Microglial M1/M2 polarization and metabolic states. *Br. J. Pharmacol.* **2016**, *173*, 649–665. [CrossRef]
15. Kim, S.; Son, Y. Astrocytes Stimulate Microglial Proliferation and M2 Polarization In Vitro through Crosstalk between Astrocytes and Microglia. *Int. J. Mol. Sci.* **2021**, *22*, 8800. [CrossRef] [PubMed]
16. Goldman, D.H.; Dykstra, T.; Smirnov, I.; Blackburn, S.M.; Da Mesquita, S.; Kipnis, J.; Herz, J. Age-associated suppression of exploratory activity during sickness is linked to meningeal lymphatic dysfunction and microglia activation. *Nat. Aging* **2022**, *2*, 704–713. [CrossRef]
17. Jayaraj, K.; Kumar, R.; Shyamasundar, S.; Arumugam, T.V.; Polepalli, J.S.; Dheen, S.T. Spatial Transcriptomic Analysis Reveals HDAC Inhibition Modulates Microglial Dynamics to Protect Against Ischemic Stroke in Mice. *Glia* **2025**, *73*, 1817–1840. [CrossRef]

18. Nirakis, N.; Dimothyra, S.; Karadima, E.; Alexaki, V.I. Metabolic regulation of immune memory and function of microglia. *Elife* **2025**, *14*, e107552. [CrossRef]
19. Ginhoux, F.; Prinz, M. Origin of microglia: Current concepts and past controversies. *Cold Spring Harb. Perspect. Biol.* **2015**, *1*, 7. [CrossRef]
20. Masuda, T.; Sankowski, R.; Staszewski, O.; Prinz, M. Microglia Heterogeneity in the Single-Cell Era. *Cell Rep.* **2020**, *30*, 1271–1281. [CrossRef] [PubMed]
21. Paolicelli, R.C.; Bolasco, G.; Pagani, F.; Maggi, L.; Scianni, M.; Panzanelli, P.; Giustetto, M.; Ferreira, T.A.; Guiducci, E.; Dumas, L.; et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* **2011**, *333*, 1456–1458. [CrossRef]
22. Colonna, M.; Butovsky, O. Microglia function in the central nervous system during health and neurodegeneration. *Annu. Rev. Immunol.* **2017**, *35*, 441–468. [CrossRef] [PubMed]
23. Salter, M.W.; Stevens, B. Microglia emerge as central players in brain disease. *Nat. Med.* **2017**, *23*, 1018–1027. [CrossRef]
24. Li, Q.; Barres, B.A. Microglia and macrophages in brain homeostasis and disease. *Nat. Rev. Immunol.* **2017**, *18*, 225–242. [CrossRef]
25. Ransohoff, R.M. How neuroinflammation contributes to neurodegeneration. *Science* **2016**, *353*, 777–783. [CrossRef]
26. Hammond, T.R.; Dufort, C.; Dissing-Olesen, L.; Giera, S.; Young, A.; Wysoker, A.; Walker, A.J.; Gergits, F.; Segel, M.; Nemesh, J.; et al. Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* **2019**, *50*, 253–271. [CrossRef]
27. Masuda, T.; Sankowski, R.; Staszewski, O.; Böttcher, C.; Amann, L.; Sagar-Scheiwe, C.; Nessler, S.; Kunz, P.; van Loo, G.; Coenen, V.A.; et al. Spatial and temporal heterogeneity of mouse and human microglia at single-cell resolution. *Nature* **2019**, *566*, 388–392. [CrossRef]
28. Clayton, K.A.; Van Enoo, A.A.; Ikezu, T. Alzheimer's Disease: The Role of Microglia in Brain Homeostasis and Proteopathy. *Front. Neurosci.* **2017**, *11*, 680. [CrossRef] [PubMed]
29. Ye, L.; Huang, Y.; Zhao, L.; Li, Y.; Sun, L.; Zhou, Y.; Qian, G.; Zheng, J.C. IL-1β and TNF-α induce neurotoxicity through glutamate production: A potential role for neuronal glutaminase. *J. Neurochem.* **2013**, *125*, 897–908. [CrossRef] [PubMed]
30. Bartra, C.; Vuraić, K.; Yuan, Y.; Codony, S.; Valdés-Quiroz, H.; Casal, C.; Slevin, M.; Máquez-Kisinousky, L.; Planas, A.M.; Griñán-Ferré, C.; et al. Microglial pro-inflammatory mechanisms induced by monomeric C-reactive protein are counteracted by soluble epoxide hydrolase inhibitors. *Int. Immunopharmacol.* **2025**, *155*, 114644. [CrossRef]
31. Keren-Shaul, H.; Spinrad, A.; Weiner, A.; Matcovitch-Natan, O.; Dvir-Szternfeld, R.; Ulland, T.K.; David, E.; Baruch, K.; Lara-Astaiso, D.; Toth, B.; et al. A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* **2017**, *169*, 1276–1290. [CrossRef]
32. Cleland, N.R.W.; Potter, G.J.; Buck, C.; Quang, D.; Oldham, D.; Neal, M.; Saviola, A.; Niemeyer, C.S.; Dobrinskikh, E.; Bruce, K.D. Altered metabolism and DAM-signatures in female brains and microglia with aging. *Brain Res.* **2024**, *1829*, 148772. [CrossRef]
33. Shimizu, T.; Prinz, M. Microglia across evolution: From conserved origins to functional divergence. *Cell. Mol. Immunol.* **2025**, *22*, 1533–1548. [CrossRef]
34. Subramaniam, S.R.; Federoff, H.J. Targeting Microglial Activation States as a Therapeutic Avenue in Parkinson's Disease. *Front. Aging Neurosci.* **2017**, *9*, 176. [CrossRef] [PubMed]
35. Li, H.; Liu, S.; Han, J.; Li, S.; Gao, X.; Wang, M.; Zhu, J.; Jin, T. Role of Toll-Like Receptors in Neuroimmune Diseases: Therapeutic Targets and Problems. *Front. Immunol.* **2021**, *12*, 777606. [CrossRef] [PubMed]
36. Song, J.; Han, K.; Wang, Y.; Qu, R.; Liu, Y.; Wang, S.; Wang, Y.; An, Z.; Li, J.; Wu, H.; et al. Microglial Activation and Oxidative Stress in PM2.5-Induced Neurodegenerative Disorders. *Antioxidants* **2022**, *11*, 1482. [CrossRef] [PubMed]
37. Lull, M.E.; Block, M.L. Microglial activation and chronic neurodegeneration. *Neurotherapeutics* **2010**, *7*, 354–365. [CrossRef]
38. Li, J.; Shui, X.; Sun, R.; Wan, L.; Zhang, B.; Xiao, B.; Luo, Z. Microglial Phenotypic Transition: Signaling Pathways and Influencing Modulators Involved in Regulation in Central Nervous System Diseases. *Front. Cell Neurosci.* **2021**, *15*, 736310. [CrossRef]
39. Liang, W.; Han, B.; Hai, Y.; Liu, Y.; Liu, X.; Yang, J.; Sun, D.; Yin, P. The Role of Microglia/Macrophages Activation and TLR4/NF-κB/MAPK Pathway in Distraction Spinal Cord Injury-Induced Inflammation. *Front. Cell Neurosci.* **2022**, *16*, 926453. [CrossRef]
40. Frederiksen, H.R.; Haukedal, H.; Freude, K. Cell Type Specific Expression of Toll-Like Receptors in Human Brains and Implications in Alzheimer's Disease. *Biomed. Res. Int.* **2019**, *2019*, 7420189. [CrossRef]
41. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Signal Transduct. Target Ther.* **2023**, *8*, 359. [CrossRef]
42. Jordão, M.J.C.; Sankowski, R.; Brendecke, S.M.; Sagar; Locatelli, G.; Tai, Y.-H.; Tay, T.L.; Schramm, E.; Armbruster, S.; Hagemeyer, N.; et al. Single-cell profiling identifies myeloid cell subsets with distinct fates during neuroinflammation. *Science* **2019**, *363*, eaat7554. [CrossRef]
43. Mathys, H.; Adaikkan, C.; Gao, F.; Young, J.Z.; Manet, E.; Hemberg, M.; De Jager, P.L.; Ransohoff, R.M.; Regev, A.; Tsai, L.-H. Temporal Tracking of Microglia Activation in Neurodegeneration at Single-Cell Resolution. *Cell Rep.* **2017**, *21*, 366–380. [CrossRef] [PubMed]

44. Scott, T.E.; Lewis, C.V.; Zhu, M.; Wang, C.; Samuel, C.S.; Drummond, G.R.; Kemp-Harper, B.K. IL-4 and IL-13 induce equivalent expression of traditional M2 markers and modulation of reactive oxygen species in human macrophages. *Sci Rep.* **2023**, *13*, 19589. [CrossRef] [PubMed]
45. Friedman, B.A.; Srinivasan, K.; Ayalon, G.; Meilandt, W.J.; Lin, H.; Huntley, M.A.; Cao, Y.; Lee, S.-H.; Haddick, P.C.; Ngu, H.; et al. Diverse Brain Myeloid Expression Profiles Reveal Distinct Microglial Activation States and Aspects of Alzheimer's Disease Not Evident in Mouse Models. *Cell Rep.* **2018**, *22*, 832–847. [CrossRef] [PubMed]
46. Streit, W.J.; Khoshbouei, H.; Bechmann, I. Dystrophic microglia in late-onset Alzheimer's disease. *Glia* **2020**, *68*, 845–854. [CrossRef]
47. Safaiyan, S.; Besson-Girard, S.; Kaya, T.; Cantuti-Castelvetri, L.; Liu, L.; Ji, H.; Schifferer, M.; Gouna, G.; Usifo, F.; Kannaiyan, N. White matter aging drives microglial diversity. *Neuron* **2021**, *109*, 1100–1117.e10. [CrossRef]
48. Yu, L.; Dong, Y.; Li, M.; Liu, H.; Yan, C.; Li, X.; Gu, Y.; Wang, L.; Xu, C.; Xu, J.; et al. Targeting microglia polarization with Chinese herb-derived natural compounds for neuroprotection in ischemic stroke. *Front. Cell Dev. Biol.* **2025**, *13*, 1580479. [CrossRef]
49. Wieczorek-Szukala, K.; Markiewicz, M.; Walczewska, A.; Zgorzynska, E. Docosahexaenoic Acid (DHA) Reduces LPS-Induced Inflammatory Response Via ATF3 Transcription Factor and Stimulates Src/Syk Signaling-Dependent Phagocytosis in Microglia. *Cell Physiol. Biochem.* **2023**, *57*, 411–425.
50. Jara, C.; Torres, A.K.; Park-Kang, H.S.; Sandoval, L.; Retamal, C.; Gonzalez, A.; Ricca, M.; Valenzuela, S.; Murphy, M.P.; Inestrosa, N.C.; et al. Curcumin Improves Hippocampal Cell Bioenergetics, Redox and Inflammatory Markers, and Synaptic Proteins, Regulating Mitochondrial Calcium Homeostasis. *Neurotox Res.* **2025**, *43*, 3. [CrossRef]
51. Jiang, M.; Wang, K.; Huang, Y.; Zhang, X.; Yang, T.; Zhan, K.; Zhao, G. Quercetin Alleviates Lipopolysaccharide-Induced Cell Oxidative Stress and Inflammatory Responses via Regulation of the TLR4-NF-κB Signaling Pathway in Bovine Rumen Epithelial Cells. *Toxins* **2023**, *15*, 512. [CrossRef] [PubMed]
52. Bissacotti, B.F.; da Silveira, M.V.; Assmann, C.E.; Copetti, P.M.; Santos, A.F.D.; Fagan, S.B.; da Rocha, J.A.P.; Schetinger, M.R.C.; Morsch, V.M.M.; Bottari, N.B.; et al. Resveratrol Alleviates Inflammatory Response Through P2X7/NLRP3 Signaling Pathway: In Silico and In Vitro Evidence from Activated Microglia. *Pharmaceuticals* **2025**, *18*, 950. [CrossRef] [PubMed]
53. Inchingolo, A.D.; Inchingolo, A.M.; Malcangi, G.; Avantario, P.; Azzollini, D.; Buongiorno, S.; Viapiano, F.; Campanelli, M.; Ciocia, A.M.; De Leonardis, N.; et al. Effects of Resveratrol, Curcumin and Quercetin Supplementation on Bone Metabolism—A Systematic Review. *Nutrients* **2022**, *14*, 3519. [CrossRef]
54. Liu, B.; Zhang, Y.; Yang, Z.; Liu, M.; Zhang, C.; Zhao, Y.; Song, C. ω-3 DPA Protected Neurons from Neuroinflammation by Balancing Microglia M1/M2 Polarizations through Inhibiting NF-κB/MAPK p38 Signaling and Activating Neuron-BDNF-PI3K/AKT Pathways. *Mar. Drugs* **2021**, *19*, 587. [CrossRef]
55. Gao, X.; Fu, S.; Wen, J.; Yan, A.; Yang, S.; Zhang, Y.; Liu, D.; He, D. Orally Administered Ginkgolide C Alleviates MPTP-Induced Neurodegeneration by Suppressing Neuroinflammation and Oxidative Stress through Microbiota-Gut-Brain Axis in Mice. *J. Agric. Food Chem.* **2024**, *72*, 22115–22131. [CrossRef]
56. Zhang, D.; Han, L.; Zhang, W.; Wang, D.; Huo, D.; Tan, X.; Su, X.; Wang, M.; Xu, J.; Cheng, J.; et al. Neuroprotective mechanisms of valproic acid and alpha-lipoic acid in ALS: A network pharmacology-based investigation. *Front. Pharmacol.* **2025**, *16*, 1681929. [CrossRef]
57. Trépanier, M.O.; Hopperton, K.E.; Orr, S.K.; Bazinet, R.P. N-3 polyunsaturated fatty acids in animal models with neuroinflammation: An update. *Eur. J. Pharmacol.* **2016**, *785*, 187–206. [CrossRef] [PubMed]
58. Javed, H.; Meeran, M.F.N.; Azimullah, S.; Bader Eddin, L.; Dwivedi, V.D.; Jha, N.K.; Ojha, S. α-Bisabolol, a Dietary Bioactive Phytochemical Attenuates Dopaminergic Neurodegeneration through Modulation of Oxidative Stress, Neuroinflammation and Apoptosis in Rotenone-Induced Rat Model of Parkinson's disease. *Biomolecules* **2020**, *10*, 1421. [CrossRef]
59. Qiao, P.; Ma, J.; Wang, Y.; Huang, Z.; Zou, Q.; Cai, Z.; Tang, Y. Curcumin Prevents Neuroinflammation by Inducing Microglia to Transform into the M2-phenotype via CaMKKβ-dependent Activation of the AMP-Activated Protein Kinase Signal Pathway. *Curr. Alzheimer Res.* **2020**, *17*, 735–752. [CrossRef]
60. Wu, S.K.; Wang, L.; Wang, F.; Zhang, J. Resveratrol improved mitochondrial biogenesis by activating SIRT1/PGC-1α signal pathway in SAP. *Sci. Rep.* **2024**, *14*, 26216. [CrossRef]
61. Wang, L.; Zhao, H.; Wang, L.; Tao, Y.; Du, G.; Guan, W.; Liu, J.; Brennan, C.; Ho, C.T.; Li, S. Effects of Selected Resveratrol Analogues on Activation and Polarization of Lipopolysaccharide-Stimulated BV-2 Microglial Cells. *J. Agric. Food Chem.* **2020**, *68*, 3750–3757. [CrossRef]
62. Huang, W.; Zhong, Y.; Gao, B.; Zheng, B.; Liu, Y. Nrf2-mediated therapeutic effects of dietary flavones in different diseases. *Front. Pharmacol.* **2023**, *14*, 1240433. [CrossRef]
63. Hadad, N.; Levy, R. Combination of EPA with Carotenoids and Polyphenol Synergistically Attenuated the Transformation of Microglia to M1 Phenotype Via Inhibition of NF-κB. *Neuromolecular. Med.* **2017**, *19*, 436–451. [CrossRef]
64. Ulland, T.K.; Song, W.M.; Huang, S.C.-C.; Ulrich, J.D.; Sergushichev, A.; Beatty, W.L.; Loboda, A.A.; Zhou, Y.; Cairns, N.J.; Kambal, A.; et al. TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. *Cell* **2017**, *170*, 649–663.e13. [CrossRef]

65. Zhang, M.; Tang, Z. Therapeutic potential of natural molecules against Alzheimer's disease via SIRT1 modulation. *Biomed. Pharmacother.* **2023**, *161*, 114474. [CrossRef]
66. Peña-Ortega, F. Microglial modulation of neuronal network function and plasticity. *J. Neurophysiol.* **2025**, *133*, 661–680. [CrossRef]
67. Kraft, A.W.; Hu, X.; Yoon, H.; Yan, P.; Xiao, Q.; Wang, Y.; Gil, S.C.; Brown, J.; Wilhelmsson, U.; Restivo, J.L.; et al. Attenuating astrocyte activation accelerates plaque pathogenesis in APP/PS1 mice. *FASEB J.* **2013**, *27*, 187–198. [CrossRef] [PubMed]
68. Li, X.; Li, Y.; Jin, Y.; Zhang, Y.; Wu, J.; Xu, Z.; Huang, Y.; Cai, L.; Gao, S.; Liu, T.; et al. Transcriptional and epigenetic decoding of the microglial aging process. *Nat. Aging* **2023**, *3*, 1288–1311. [CrossRef] [PubMed]
69. Lima, M.N.; Barbosa-Silva, M.C.; Maron-Gutierrez, T. Microglial Priming in Infections and Its Risk to Neurodegenerative Diseases. *Front. Cell Neurosci.* **2022**, *16*, 878987. [CrossRef] [PubMed]
70. Ritzel, R.M.; Li, Y.; Jiao, Y.; Lei, Z.; Doran, S.J.; He, J.; Shahror, R.A.; Henry, R.J.; Khan, R.; Tan, C.; et al. Brain injury accelerates the onset of a reversible age-related microglial phenotype associated with inflammatory neurodegeneration. *Sci. Adv.* **2023**, *9*, eadd1101. [CrossRef]
71. Kobayashi, K.; Imagama, S.; Ohgomori, T.; Hirano, K.; Uchimura, K.; Sakamoto, K.; Hirakawa, A.; Takeuchi, H.; Suzumura, A.; Ishiguro, N.; et al. Minocycline selectively inhibits M1 polarization of microglia. *Cell Death Dis.* **2013**, *4*, e525. [CrossRef] [PubMed]
72. E Hickman, S.; Kingery, N.D.; Ohsumi, T.K.; Borowsky, M.L.; Wang, L.-C.; Means, T.K.; El Khoury, J. The microglial sensome revealed by direct RNA sequencing. *Nat. Neurosci.* **2013**, *16*, 1896–1905. [CrossRef]
73. Prinz, M.; Priller, J.; Sisodia, S.S.; Ransohoff, R.M. Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. *Nat. Neurosci.* **2011**, *14*, 1227–1235. [CrossRef]
74. Au, W.H.; Miller-Fleming, L.; Sanchez-Martinez, A.; Lee, J.A.; Twyning, M.J.; A Prag, H.; Raik, L.; Allen, S.P.; Shaw, P.J.; Ferraiuolo, L.; et al. Activation of the Keap1/Nrf2 pathway suppresses mitochondrial dysfunction, oxidative stress, and motor phenotypes in C9orf72 ALS/FTD models. *Life Sci. Alliance* **2024**, *7*, e202402853. [CrossRef] [PubMed]
75. Wang, H.; Chen, D.; Li, Y.; Gao, X.; Li, R.; Ma, T.; Zhang, Z. Molecular Mechanism of the Protective Effects of M2 Microglia on Neurons: A Review Focused on Exosomes and Secretory Proteins. *Neurochem. Res.* **2022**, *47*, 3556–3564. [CrossRef]
76. Augusto-Oliveira, M.; Arrifano, G.d.P.; Leal-Nazaré, C.G.; Chaves-Filho, A.; Santos-Sacramento, L.; Lopes-Araujo, A.; Tremblay, M.; Crespo-Lopez, M.E. Morphological diversity of microglia: Implications for learning, environmental adaptation, ageing, sex differences and neuropathology. *Neurosci. Biobehav. Rev.* **2025**, *172*, 106091. [CrossRef] [PubMed]
77. Rim, C.; You, M.J.; Nahm, M.; Kwon, M.S. Emerging role of senescent microglia in brain aging-related neurodegenerative diseases. *Transl. Neurodegener.* **2024**, *13*, 10. [CrossRef]
78. Maassen, A.; Steciuk, J.; Wilga, M.; Szurmak, J.; Garbicz, D.; Sarnowska, E.; Sarnowski, T.J. SWI/SNF-type complexes-transcription factor interplay: A key regulatory interaction. *Cell. Mol. Biol. Lett.* **2025**, *30*, 30. [CrossRef]
79. Scholz, R.; Brösamle, D.; Yuan, X.; Beyer, M.; Neher, J.J. Epigenetic control of microglial immune responses. *Immunol. Rev.* **2024**, *323*, 209–226. [CrossRef]
80. Sunna, S.; Bowen, C.A.; Ramelow, C.C.; Santiago, J.V.; Kumar, P.; Rangaraju, S. Advances in proteomic phenotyping of microglia in neurodegeneration. *Proteomics* **2023**, *23*, e2200183. [CrossRef]
81. Saeki, K.; Ozato, K. Transcription factors that define the epigenome structures and transcriptomes in microglia. *Exp. Hematol.* **2025**, *149*, 104814. [CrossRef]
82. Chamera, K.; Trojan, E.; Szuster-Głuszczak, M.; Basta-Kaim, A. The Potential Role of Dysfunctions in Neuron-Microglia Communication in the Pathogenesis of Brain Disorders. *Curr. Neuropharmacol.* **2019**, *18*, 408–430. [CrossRef] [PubMed]
83. Sofroniew, M.V. Astrocyte Reactivity: Subtypes, States, and Functions in CNS Innate Immunity. *Trends Immunol.* **2020**, *41*, 758–770. [CrossRef] [PubMed]
84. Escartin, C.; Galea, E.; Lakatos, A.; O'cAllaghan, J.P.; Petzold, G.C.; Serrano-Pozo, A.; Steinhäuser, C.; Volterra, A.; Carmignoto, G.; Agarwal, A.; et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nature* **2017**, *541*, 481–487. [CrossRef] [PubMed]
85. Liddelow, S.A.; Guttenplan, K.A.; Clarke, L.E.; Bennett, F.C.; Bohlen, C.J.; Schirmer, L.; Bennett, M.L.; Münch, A.E.; Chung, W.-S.; Peterson, T.C.; et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **2017**, *541*, 481–487. [CrossRef]
86. Baik, S.H.; Kang, S.; Lee, W.; Choi, H.; Chung, S.; Kim, J.-I.; Mook-Jung, I. A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease. *Cell Metab.* **2019**, *30*, 493–507.e6. [CrossRef]
87. Habib, N.; McCabe, C.; Medina, S.; Varshavsky, M.; Kitsberg, D.; Dvir-Szternfeld, R.; Green, G.; Dionne, D.; Nguyen, L.; Marshall, J.L.; et al. Disease-associated astrocytes in Alzheimer's disease and aging. *Nat. Neurosci.* **2020**, *23*, 701–706. [CrossRef]
88. Holtman, I.R.; Raj, D.D.; Miller, J.A.; Schaafsma, W.; Yin, Z.; Brouwer, N.; Wes, P.D.; Möller, T.; Orre, M.; Kamphuis, W.; et al. Induction of a common microglia gene expression signature by aging and neurodegenerative conditions: A co-expression meta-analysis. *Acta Neuropathol. Commun.* **2015**, *3*, 31. [CrossRef]
89. Wu, Y.; Eisel, U.L.M. Microglia-Astrocyte Communication in Alzheimer's Disease. *J. Alzheimer's Dis.* **2023**, *95*, 785–803. [CrossRef]

90. Chen, W.; Mao, T.; Ma, R.; Xiong, Y.; Han, R.; Wang, L. The role of astrocyte metabolic reprogramming in ischemic stroke [Review]. *Int. J. Mol. Med.* **2025**, *55*, 49. [CrossRef]
91. Dar, N.J.; Bhat, J.A.; John, U.; Bhat, S.A. Neuroglia in Neurodegeneration: Exploring Glial Dynamics in Brain Disorders. *Neuroglia* **2024**, *5*, 488–504. [CrossRef]
92. Quan, L.; Uyeda, A.; Muramatsu, R. Central nervous system regeneration: The roles of glial cells in the potential molecular mechanism underlying remyelination. *Inflamm. Regen.* **2022**, *42*, 7. [CrossRef] [PubMed]
93. Santos, E.N.; Fields, R.D. Regulation of myelination by microglia. *Sci. Adv.* **2021**, *7*, 1131. [CrossRef]
94. Dwivedi, S.; Ranjan, S.; Das, S.; Kumari, J.; Singh, S. Role of growth factors and their interplay during oligodendroglial differentiation and maturation. *Cytokine Growth Factor Rev.* **2025**, *84*, 47–58. [CrossRef]
95. Mosser, C.A.; Baptista, S.; Arnoux, I.; Audinat, E. Microglia in CNS development: Shaping the brain for the future. *Prog. Neurobiol.* **2017**, *149–150*, 1–20. [CrossRef] [PubMed]
96. Hattori, Y. The multifaceted roles of embryonic microglia in the developing brain. *Front. Cell Neurosci.* **2023**, *17*, 988952. [CrossRef] [PubMed]
97. Fujita, Y.; Yamashita, T. Neuroprotective function of microglia in the developing brain. *Neuronal Signal* **2021**, *5*, NS20200024. [CrossRef]
98. Tong, C.K.; Vidyadaran, S. Role of microglia in embryonic neurogenesis. *Exp. Biol. Med.* **2016**, *241*, 1669–1675. [CrossRef]
99. Cserép, C.; Pósfai, B.; Lénárt, N.; Fekete, R.; László, Z.I.; Lele, Z.; Orsolits, B.; Molnár, G.; Heindl, S.; Schwarcz, A.D.; et al. Microglia monitor and protect neuronal function through specialized somatic purinergic junctions. *Science* **2020**, *367*, 528–537. [CrossRef]
100. Cornell, J.; Salinas, S.; Huang, H.Y.; Zhou, M. Microglia regulation of synaptic plasticity and learning and memory. *Neural Regen. Res.* **2021**, *17*, 705.
101. Béchade, C.; Cantaut-Belarif, Y.; Bessis, A. Microglial control of neuronal activity. *Front. Cell Neurosci.* **2013**, *7*, 42900. [CrossRef]
102. Kumaraguru, S.; Morgan, J.; Wong, F.K. Activity-dependent regulation of microglia numbers by pyramidal cells during development shape cortical functions. *Sci. Adv.* **2025**, *11*, eadq5842. [CrossRef]
103. Cipriano, A.; Viviano, M.; Feoli, A.; Milite, C.; Sarno, G.; Castellano, S.; Sbardella, G. NADPH Oxidases: From Molecular Mechanisms to Current Inhibitors. *J. Med. Chem.* **2023**, *66*, 11632–11655. [CrossRef]
104. Forrester, S.J.; Kikuchi, D.S.; Hernandes, M.S.; Xu, Q.; Griendling, K.K. Reactive Oxygen Species in Metabolic and Inflammatory Signaling. *Circ. Res.* **2018**, *122*, 877–902. [CrossRef]
105. Meng, L.; Liu, S.; Luo, J.; Tu, Y.; Li, T.; Li, P.; Yu, J.; Shi, L. Oxidative stress and reactive oxygen species in otorhinolaryngological diseases: Insights from pathophysiology to targeted antioxidant therapies. *Redox Rep.* **2025**, *30*, 2458942. [CrossRef]
106. Ansari, M.A.; Al-Jarallah, A.; Rao, M.S.; Babiker, A.; Bensalamah, K. Upregulation of NADPH-oxidase, inducible nitric oxide synthase and apoptosis in the hippocampus following impaired insulin signaling in the rats: Development of sporadic Alzheimer's disease. *Brain Res.* **2024**, *1834*, 148890. [CrossRef] [PubMed]
107. Hamzeh, O.; Rabiei, F.; Shakeri, M.; Parsian, H.; Saadat, P.; Rostami-Mansoor, S. Mitochondrial dysfunction and inflammasome activation in neurodegenerative diseases: Mechanisms and therapeutic implications. *Mitochondrion* **2023**, *73*, 72–83. [CrossRef] [PubMed]
108. Lin, H.; Xiong, W.; Fu, L.; Yi, J.; Yang, J. Damage-associated molecular patterns [DAMPs] in diseases: Implications for therapy. *Mol. Biomed.* **2025**, *6*, 60. [CrossRef] [PubMed]
109. Naddaf, E.; Nguyen, T.K.O.; Watzlawik, J.O.; Gao, H.; Hou, X.; Fiesel, F.C.; Mandrekar, J.; Kokesh, E.; Harmsen, W.S.; Lanza, I.R.; et al. NLRP3 Inflammasome Activation and Altered Mitophagy Are Key Pathways in Inclusion Body Myositis. *J. Cachexia Sarcopenia Muscle* **2024**, *16*, e13672. [CrossRef]
110. Yu, H.; Ren, K.; Jin, Y.; Zhang, L.; Liu, H.; Huang, Z.; Zhang, Z.; Chen, X.; Yang, Y.; Wei, Z. Mitochondrial DAMPs: Key mediators in neuroinflammation and neurodegenerative disease pathogenesis. *Neuropharmacology* **2025**, *264*, 110217. [CrossRef]
111. Paik, S.; Kim, J.K.; Shin, H.J.; Park, E.J.; Kim, I.S.; Jo, E.K. Updated insights into the molecular networks for NLRP3 inflammasome activation. *Cell. Mol. Immunol.* **2025**, *22*, 563–596. [CrossRef] [PubMed]
112. Smith, A.N.; Shaughness, M.; Collier, S.; Hopkins, D.; Byrnes, K.R. Therapeutic targeting of microglia mediated oxidative stress after neurotrauma. *Front. Med.* **2022**, *9*, 1034692. [CrossRef] [PubMed]
113. Wang, L.; Yu, C.C.; Liu, X.Y.; Deng, X.N.; Tian, Q.; Du, Y.J. Epigenetic Modulation of Microglia Function and Phenotypes in Neurodegenerative Diseases. *Neural Plast.* **2021**, *2021*, 9912686. [CrossRef]
114. Qin, J.; Ma, Z.; Chen, X.; Shu, S. Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. *Front. Neurol.* **2023**, *14*, 1103416. [CrossRef] [PubMed]
115. Heneka, M.T.; Kummer, M.P.; Stutz, A.; Delekate, A.; Schwartz, S.; Vieira-Saecker, A.; Griep, A.; Axt, D.; Remus, A.; Tzeng, T.C.; et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* **2013**, *493*, 674–678. [CrossRef]

116. Zhao, M.-Y.; Ye, C.-Y.; Liu, Y.-C.; Wang, X.-M.; Fu, J.-C.; Liu, X.-Y.; Zhu, R.; Li, Y.-Z.; Tian, Q. Role of meningeal lymphatic vessels in brain homeostasis. *Front. Immunol.* **2025**, *16*, 1593630. [CrossRef]
117. Lall, D.; Baloh, R.H. Microglia and C9orf72 in neuroinflammation and ALS and frontotemporal dementia. *J. Clin. Investig.* **2017**, *127*, 3250–3258. [CrossRef]
118. De Marchi, F.; Tondo, G.; Corrado, L.; Menegon, F.; Aprile, D.; Anselmi, M.; D'Alfonso, S.; Comi, C.; Mazzini, L. Neuroinflammatory Pathways in the ALS-FTD Continuum: A Focus on Genetic Variants. *Genes* **2023**, *14*, 1658. [CrossRef]
119. MacLean, M.; Juranek, J.; Cuddapah, S.; López-Díez, R.; Ruiz, H.H.; Hu, J.; Frye, L.; Li, H.; Gugger, P.F.; Schmidt, A.M. Microglia RAGE exacerbates the progression of neurodegeneration within the SOD1G93A murine model of amyotrophic lateral sclerosis in a sex-dependent manner. *J. Neuroinflam.* **2021**, *18*, 139. [CrossRef]
120. Gunner, G.; Basu, H.; Lu, Y.; Bergstresser, M.; Neel, D.; Choi, S.Y.; Chiu, I.M. Gasdermin D is activated but does not drive neurodegeneration in SOD1 G93A model of ALS: Implications for targeting pyroptosis. *Neurobiol. Dis.* **2024**, *214*, 107048. [CrossRef]
121. Catale, C.; Garel, S. Microglia in early brain development: A window of opportunity. *Curr. Opin. Neurobiol.* **2025**, *93*, 103062. [CrossRef]
122. Rogerson-Wood, L.; Sawatari, A.; Leamey, C.A. Microglia: Mediators of experience-driven corrective neuroplasticity. *IBRO Neurosci. Rep.* **2025**, *19*, 91–100. [CrossRef]
123. Arrant, A.E.; Filiano, A.J.; Patel, A.R.; Hoffmann, M.Q.; Boyle, N.R.; Kashyap, S.N.; Onyilo, V.C.; Young, A.H.; Roberson, E.D. Reduction of microglial progranulin does not exacerbate pathology or behavioral deficits in neuronal progranulin-insufficient mice. *Neurobiol. Dis.* **2019**, *124*, 152–162. [CrossRef]
124. Zhou, Y.; Ulland, T.K.; Colonna, M. TREM2-Dependent Effects on Microglia in Alzheimer's Disease. *Front. Aging Neurosci.* **2018**, *10*, 202. [CrossRef]
125. Adaikkan, C.; Islam, M.R.; Bozzelli, P.L.; Sears, M.; Parro, C.; Pao, P.C.; Sun, N.; Kim, T.; Abdelaal, K.; Sedgwick, M.; et al. A multimodal approach of microglial CSF1R inhibition and GENUS provides therapeutic effects in Alzheimer's disease mice. *bioRxiv* **2025**. [CrossRef]
126. Wang, S.; Weyer, M.P.; Hummel, R.; Wilken-Schmitz, A.; Tegeder, I.; Schäfer, M.K.E. Selective neuronal expression of progranulin is sufficient to provide neuroprotective and anti-inflammatory effects after traumatic brain injury. *J. Neuroinflam.* **2024**, *21*, 257. [CrossRef] [PubMed]
127. Kuhn, M.K.; Proctor, E.A. Microglial Drivers of Alzheimer's Disease Pathology: An Evolution of Diverse Participating States. *Proteins* **2025**, *93*, 1330–1348. [CrossRef]
128. Chinnathambi, S. α-Linolenic Acid Vesicles-Mediated Tau Internalization in Microglia. *Methods Mol Biol.* **2024**, *2816*, 117–128. [PubMed]
129. Chen, K.; Li, F.; Zhang, S.; Chen, Y.; Ikezu, T.C.; Li, Z.; Martens, Y.A.; Qiao, W.; Meneses, A.; Zhu, Y.; et al. Enhancing TREM2 expression activates microglia and modestly mitigates tau pathology and neurodegeneration. *J. Neuroinflam.* **2025**, *22*, 93. [CrossRef] [PubMed]
130. Ramakrishnan, G.S.; Berry, W.L.; Pacherille, A.; Kerr, W.G.; Chisholm, J.D.; Pedicone, C.; Humphrey, M.B. SHIP inhibition mediates select TREM2-induced microglial functions. *Mol. Immunol.* **2024**, *170*, 35–45. [CrossRef]
131. Daudelin, D.; Westerhaus, A.; Zhang, N.; Leyder, E.; Savonenko, A.; Sockanathan, S. Loss of GDE2 leads to complex behavioral changes including memory impairment. *Behav. Brain Funct.* **2024**, *20*, 7. [CrossRef] [PubMed]
132. Boyanova, S.; Banks, G.; Lipina, T.V.; Bains, R.S.; Forrest, H.; Stewart, M.; Carcolé, M.; Milioto, C.; Isaacs, A.M.; Wells, S.E.; et al. Multi-modal comparative phenotyping of knock-in mouse models of frontotemporal dementia/amyotrophic lateral sclerosis. *Dis. Model Mech.* **2025**, *18*, dmm052324. [CrossRef] [PubMed]