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Targeting brain colony stimulating factor 1 receptor for phagocytic microglia reprogramming as a potential strategy against brain inflammation

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Microglia play a multifaceted role in modulating the regenerative landscape in the central nervous system across a spectrum of neurological conditions, including neurodegenerative disease, ageing-related cognitive decline, neurodevelopmental and metabolic disorders, and cancer.

Microglia can sense alterations in neuronal activity, responding to both hypoactivity and hyperactivity, which is vital for preserving neural circuit integrity. Indeed, emerging evidence suggests that, beyond immune surveillance, microglia modulate neuronal function through calcium signaling and the release of signaling molecules, influencing both physiological and pathological states. In fact, microglia is crucial in shaping neural circuits by regulating synaptic plasticity, a fundamental process for cognitive function often impaired in various neurological disorders (Umpierre and Wu, 2021).

The main regulator of microglial development, homeostasis, and survival in the central nervous system is colony stimulating factor 1 receptor (CSF1R), a key tyrosine kinase transmembrane receptor with two ligands, the colony stimulating factor 1 (CSF1) and interleukin 34. Upon ligand binding, CSF1R dimerizes and undergoes autophosphorylation, activating intracellular signaling cascades that regulate microglial biology. The CSF1R plays a critical role in microglial fitness, which encompasses their proliferation, survival, and homeostasis.

CSF1R pathway dysfunction has also been implicated in several neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, frontotemporal dementia, amyotrophic lateral sclerosis, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, and brain tumors.

Together with Triggering receptor expressed on myeloid cells 2 (TREM2), a coreceptor exclusively expressed by brain microglia and strongly associated with AD risk, CSF1R initiates a cascade leading to sustained mammalian target of rapamycin activity, lysosomal activity, and phagocytosis, of relevance for misfolded protein clearance and neuronal plasticity in neuropathology (Han et al., 2022).

Conversely, the CSF1-dependent increase in proliferation of microglial cells around amyloid plaques has been described at the preclinical level in AD mouse model and confirmed in post-mortem brain samples from AD patients (Mancuso et al., 2019; Han et al., 2022).

Although microglia are essential for responding to brain injuries and regulating neuronal activity during development and in adulthood, their overactivation can result in detrimental effects, contributing to chronic neurodegeneration, abnormal synaptic pruning during development or following traumatic brain injury. In a mouse model of diet-induced obesity, CSF1R inhibition mitigates metabolic dysregulation, brain inflammation, and defects in hippocampal synaptic plasticity (Elmore et al., 2015).

In line, pharmacological depletion of developmental microglia using a CSF1R inhibitor restored neurotransmission and spine density in hippocampal neurons, suggesting that excessive microglia activation is detrimental to brain functions. This duality underscores the necessity of a balanced approach in targeting microglial functions for therapeutic interventions.

The blockade of microglial proliferation, without compromising survival, has also been shown to improve memory and behavioral tasks, as well as prevent synaptic degeneration in APP/PS1 mice. Prolonged inhibition of CSF1R by GW2580 in APP/PS1 mice resulted in a shift of the microglial inflammatory profile towards an anti-inflammatory phenotype. Pharmacological targeting of CSF1R with inhibitors, such as PLX3397 and JNJ-527, can lead to the depletion of approximately 60% of microglia in tauopathy models. This reduction in neuroinflammation and pathogenic tau accumulation suggests that partial depletion could be beneficial, as a subset of resilient microglia may retain protective functions.

Chronic inhibition of CSF1R exhibits promising neuroprotective effects in various neurodegenerative disease models and is currently undergoing clinical investigation based on its preclinical evidence of neuroprotection. In tauopathy mouse models, CSF1R inhibitors have demonstrated reduced pathogenic tau accumulation, improved behavioral outcomes, and extended lifespan.

Several studies based on genetic or pharmacological depletion/repopulation of inflamed microglia by a more homeostatic/reactive microglia population showed improved amyloid clearance and reduced neuroinflammation, pinpointing brain microglia deletion as a promising route for neurotherapy (Olmos-Alonso et al., 2016; Pons et al., 2021; Tahmasebi et al., 2023; Kodali et al., 2025). However, more recent findings pinpoint that neuroprotection may also occur without complete microglial depletion.

In amyotrophic lateral sclerosis mouse models ($SOD1^{G93A}$), treatment with the CSF1R inhibitor GW2580 reduced activated microglia, attenuated motor deficits, and extended survival by 12%. The effects appear to involve both central microglial modulation and peripheral immune cell reduction (Elmore et al., 2015). In line, an open-label phase 2 clinical trial is ongoing to evaluate the safety and tolerability of the CSF1R inhibitor BLZ945 in amyotrophic lateral sclerosis patients (ClinicalTrials.gov identifier: NCT04066244).

In Parkinson's disease mouse models induced through injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, CSF1R and its ligand CSF-1 are upregulated in affected brain regions. The treatment with GW2580 reduces microglial proliferation, neuroinflammation, dopaminergic neuron loss, and motor deficits, indicating preclinical evidence of neuroprotection via microglial modulation (Neal et al., 2020). Interestingly, in prion disease models, CSF1R inhibition by JNJ-40346527 demonstrated a good target engagement and reduced microglial proliferation, supporting its potential clinical application in AD and related neurodegenerative diseases (Mancuso et al., 2019).

Indeed, the short-term effect of PLX3397, a highly specific and efficient *in vivo* CSF1R inhibitor, was studied in a well-characterized amyloid-based AD model. PLX3397 was found to cause microglial activation towards a phagosome-enriched microglial phenotype within 3 weeks of treatment, without affecting proliferation or survival (Sosna et al., 2018). Further, CSF1R inhibition by PLX3397 or El-1071 fosters cognition by reducing inflammation in favor of homeostatic microglia in the aged mouse brain and in the 5×TgAD mouse model, respectively (Strackeljan et al., 2025; Tamayanti et al., 2025).

In a recent preclinical study using a 3D brain model of AD, we investigated the short-term effect of non-depleting low level (1 μM, 1 hour) of the CSF1R inhibitor PLX3397, also known as Pexidartinib. We found microglial activation toward a pro-phagocytic phenotype, in the absence of any effect on proliferation or survival, following PLX3397 treatment of amyloid-based hippocampal brain slices. Beyond this morphological shift reducing the typically inflammatory rod-like microglia, upon PLX3397 microglia were more efficient in amyloid clearance, and restored physiological pruning of glutamatergic spines, resulting in restoration of synaptic plasticity. The impact of CSF1R inhibition by PLX3397 observed in our experimental conditions supported a rapid metabolic change induced by CSF1R signaling pathway blockage, resulting in improved amyloid clearance and related rescue of physiological glutamatergic plasticity observed (Piccioni et al., 2024).

The most intriguing question raised by these findings is whether the transient suppression of the CSF1R pathway may be used to target essential metabolic downstream molecules, thus redirecting microglial metabolism and instructing the switch from an inflammatory ramified microglia to a more ameboid-like prophagocytic state.

Thus, understanding microglial states in response to pharmacological manipulation can inform therapeutic strategies for conditions such as AD and Parkinson's disease, where neuroinflammation plays a pivotal role. In particular, the intricate interplay between microglial metabolic states, CSF1R signaling, and synaptic plasticity represents an area of research with substantial clinical implications.

Microglial cells can master the neuroinflammatory response (Umpierre and Wu, 2021) due to their rapid change in shape, allowing them to extend processes toward injury sites only within minutes after brain damage, driven by signals such as adenosine triphosphate (ATP) released from damaged cells. These morphological adaptations, possibly relatable to different microglial states, are essential for their migration and activation in response to various pathological conditions.

Microglial phenotypes exhibit distinct variations depending on the predominant metabolic pathway: oxidative phosphorylation (OXPHOS) or glycolysis (**Figure 1**). Homeostatic microglia primarily rely on mitochondrial OXPHOS for energy production, a highly efficient process in ATP generation that underpins microglial surveillance and maintenance functions under normal brain conditions (Huang et al., 2024). This metabolic state is often associated with a slightly ramified phenotype and reduced inflammatory activity, as well as steady energy demands.

Upon activation by inflammatory stimuli (e.g., lipopolysaccharide), pro-inflammatory microglia undergo a metabolic reprogramming from OXPHOS to aerobic glycolysis. This metabolic switch supports rapid ATP production and provides the necessary metabolic intermediates for cell growth, cytokine production, and reactive oxygen species generation. Glycolysis is less efficient compared to OXPHOS, but more rapid, enabling microglia to meet the high energy and biosynthetic demands of an inflammatory response. This phenotype is characterized by increased glucose uptake mediated by upregulated GLUT1 and increased production of pro-inflammatory cytokines (Huang et al., 2024). The metabolic switch is regulated by signaling pathways including mammalian target of rapamycin and hypoxia-inducible factor-1α, which promote glycolytic enzyme expression and suppress mitochondrial respiration during inflammation. Glycolysis provides rapid ATP and biosynthetic precursors essential for microglial proliferation and inflammatory mediator synthesis (Huang et al., 2024). In contrast, anti-inflammatory or reparative microglia exhibit enhanced mitochondrial respiration and OXPHOS, supporting functions such as phagocytosis and brain repair mechanisms, including synaptic remodeling and myelination. Microglia dynamically reprogram their metabolism, switching from mitochondrial OXPHOS in resting or anti-inflammatory states to glycolysis upon pro-inflammatory activation. This metabolic switch enables microglia to meet distinct bioenergetic and biosynthetic demands corresponding to their functional phenotypes. This metabolic flexibility is crucial for microglial functional plasticity and is implicated in neurodegenerative diseases and brain injury recovery (Huang et al., 2024).

CSF1R signaling is fundamental for microglial survival and proliferation, processes that are energetically demanding. While direct mechanistic links between CSF1R signaling and microglial metabolic reprogramming await to be elucidated, several points of intersection are evident. CSF1R pathway is promoted during proliferative and inflammatory states, when microglia shift toward glycolysis. This influences not only proliferation but potentially also the inflammatory metabolic state, as the

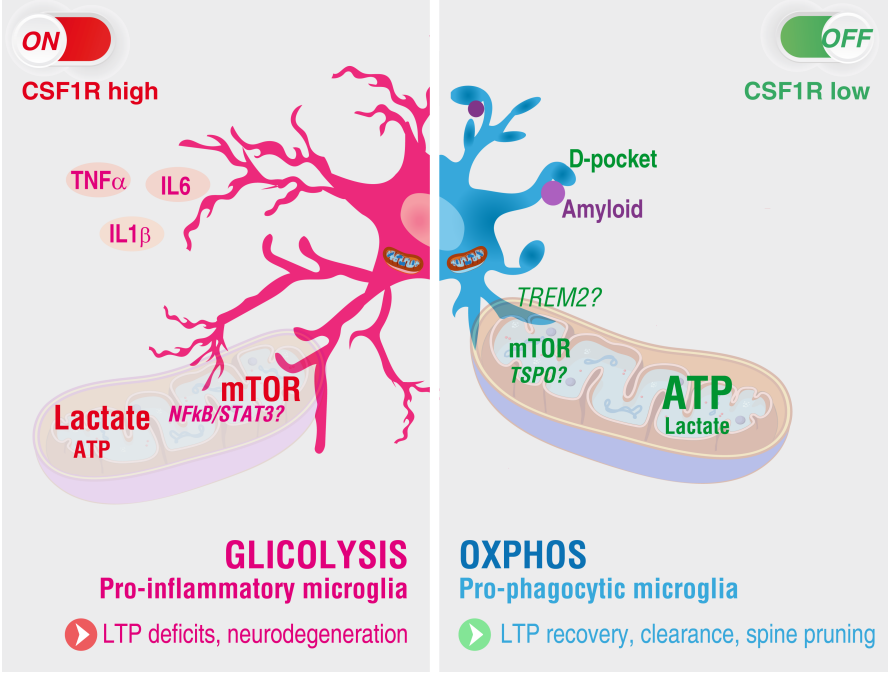

Figure 1 | **Graphical representation of the suggested CSF1R pathway and its modulation of the morpho-functional microglia phenotype through OXPHOS *versus* glycolytic metabolism control.**
The figure was realized by vectorial images from "Vecteezy" under Creative Common Attribution 4.0 International (CC BY 4.0). ATP: Adenosine triphosphate; CSF1R: colony stimulating factor 1 receptor; HK2: hexokinase 2; IL-1β (IL 1beta): interleukin 1 beta; IL6: interleukin 6; LTP: long-term potentiation; mTOR: mechanistic target of rapamycin; NFκB (NFkB): nuclear factor kappa-light-chain-enhancer of activated B cells; OXPHOS: oxidative phosphorylation; STAT (likely STAT3): signal transducer and activator of transcription; TNFα (TNF alpha): tumor necrosis factor alpha; TREM2: triggering receptor expressed on myeloid cells 2; TSPO: translocator protein.

synthesis and release of inflammatory mediators, like interleukins, require metabolic adaptation (Huang et al., 2024).

In the last decade, accumulating evidence has pinpointed both direct and indirect impact of the CSF1R pathway on microglia phenotype acquisition and reprogramming following insult.

Morphological analyses conducted on brain microglia depletion via chronic settings of CSF1R inhibition (intraperitoneal treatment/diet with 0.5 mg/kg body weight; 3 weeks) revealed a marked increase in cell body size and the thickness of processes characteristic of a more phagocytotic phenotype (**Additional Table 1**). Further, there was a reduction in the number of branches per microglia, with a stable expression of the IBA1 microglial marker in few brain microglial cells surviving the CSF1R chronic inhibition. In line with these findings, a mild inhibition of CSF1R pathway is associated with microglia survival and a transition toward a phagocytic morphology in haploinsufficient *csf1r*$^{+/-}$ mice, microglial-conditional *csf1r*$^{-/-}$ mice, hypomorphic *csf1r*FIRE$^{-/-}$ mice and in mice with rapid and low-grade CSF1R inhibition (300 mg/kg, PLX5622), as compared to the depleting dose (1200 mg/Kg, PLX5622) (Elmore et al., 2015).

Recent literature has demonstrated that CSF1R directly binds TREM2 for its regulated shedding, as also seen by co-immunoprecipitation (Cheng et al., 2021). They jointly regulate homeostatic microglial signaling and survival, establishing distinct signaling pathways (e.g., TREM2 via DAP12 and CSF1R via Akt). These pathways influence phenotype transitions, including the switch from an anti-inflammatory state to an inflammatory state. In the absence of CSF1R signaling, TREM2 has been shown to increase its expression and influence microglial shape. Conversely, CSF1R inhibition in TREM2-deficient contexts might affect survival without conclusive evidence of beneficial phenotype switching.

In conclusion, the CSF1R pathway is essential for microglial survival and function, particularly during inflammatory conditions or injury. Given its therapeutic potential in AD, Parkinson's disease, multiple sclerosis, and traumatic brain injury, targeting CSF1R is being explored as a clinical approach. During neuroinflammation and neurodegeneration, microglia undergo metabolic reprogramming, energetically transitioning from OXPHOS to glycolysis, which is intertwined with their activation state and may be influenced by CSF1R signaling. It is worth noting that while inhibition of activated microglia protects myelin integrity in demyelinating conditions such as multiple sclerosis, sustained CSF1R inhibition can impair myelin growth and maintenance, as microglia support myelin sheath formation and pruning through the CSF1R pathway (McNamara et al., 2023). Several CSF1R inhibitors have been tested in clinical trials for various conditions, including neurodegenerative diseases, with no overt immune dysfunction reported, supporting their safety profile (Han et al., 2022). In 2019, the U.S. Food and Drug Administration approved the CSF1R inhibitor vimseltinib (Romvimza; ClinicalTrials.gov, NCT05059262) and pexidartinib (Turalio; ClinicalTrials.gov, NCT02371369) for rare non-cancerous joint tumors, reflecting the clinical feasibility of targeting CSF1R. However, the clinical limitations and significant off-target side effects associated with chronic systemic CSF1R inhibition demand the identification of novel related signaling/metabolic targets for the fine-tuning of microglial phenotype-function, as well as of selected biomarkers/tracers for safety monitoring (e.g., TREM2 or TSPO radioligand for PET imaging; ^{11}C,^{18}F CSF1R inhibitors, including ^{11}C-GW2580), both fundamental for developing disease-modifying approaches for the treatment of neurodegenerative diseases.

Elucidating the precise mechanism by which distinct microglial modulation strategies influence neuronal survival across various disease contexts can pave the way for innovative, effective, and transformative therapies for a wide spectrum of neurological conditions.

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Additional file:
Additional Table 1: *Phenotypic switch of microglia under mild CSF1R inhibition and in hypomorphic genetic models.*

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