INNOVAPATH™
The Premier Journal Bridging Discovery & Innovation

Commentary
https://doi.org/10.63501/azz6za12

Microglial Metabolic Reprogramming: The Missing Link in Chronic Neurodegeneration

Rimsha Maqsood[1,2], Areeba Mushtaq[1], Kainat Nawaz[1], Ezza Ikram[1], Abdul Ghaffar Majeed[1]

[1]Quaid-e-Azam Medical College, Bahawalpur, Pakistan.

[2]Corresponding Author Email: Rimshamaqsood579@gmail.com

ABSTRACT:

Background: Microglial activation and sustained neuroinflammation are central features of chronic neurodegenerative diseases. Emerging evidence indicates that microglial function is tightly linked to intracellular metabolic state, with shifts between oxidative phosphorylation (OXPHOS) and glycolysis shaping inflammatory output, phagocytosis, and neurotoxicity.

Objective: To synthesize mechanistic, translational, and disease-specific evidence that positions microglial metabolic reprogramming as a key driver and potential therapeutic target in chronic neurodegeneration.

Methods: Narrative synthesis of preclinical and clinical studies addressing microglial metabolism, mitochondrial dysfunction, inflammasome activation, and immunometabolic interventions.

Results: Pro-inflammatory stimuli (LPS, amyloid-β, α-synuclein) induce glycolytic reprogramming in microglia, accompanied by mitochondrial dysfunction, ROS generation, and NLRP3 inflammasome activation (3,6,9). Disease-specific evidence links these metabolic shifts to impaired debris clearance and sustained cytokine release in Alzheimer's disease, Parkinson's disease, multiple sclerosis, and ALS (8–13). Age-associated metabolic remodeling primes microglia toward inflammatory phenotypes (14). Interventions targeting glycolysis, AMPK activation, or NLRP3 show consistent preclinical efficacy; however, clinical translation remains limited due to challenges in cell specificity, blood–brain barrier penetration, and temporal targeting (3,6,16).

Conclusion: Microglial immunometabolism provides a mechanistic bridge between chronic inflammation and neurodegeneration. Precision metabolic modulation of microglia, defined as selectively modulating metabolic pathways to restore homeostatic microglial functions while limiting pathological inflammatory signaling, is a promising translational strategy warranting biomarker-guided clinical evaluation.

KEYWORDS: *microglia; immunometabolism; glycolysis; oxidative phosphorylation; mitochondrial dysfunction; inflammasome; neurodegeneration*

INTRODUCTION:

Microglia are CNS-resident immune sentinels whose activation states are increasingly understood to depend on intracellular metabolic programs rather than being reducible to a simple M1/M2 binary (1,2). In peripheral myeloid cells, immunometabolic paradigms (e.g., Warburg-like glycolysis in

https://doi.org/10.63501/azz6za12

inflammatory states) have clarified how metabolism instructs effector functions; analogous, CNS-specific metabolic reprogramming in microglia appears to drive chronic neuroinflammatory phenotypes that promote neurodegenerative progression (3,4).

Importantly, emerging evidence suggests that microglial metabolism exists along a dynamic continuum rather than a strict glycolysis–OXPHOS binary. Microglia exhibit metabolic plasticity characterized by intermediate states, compartmentalized substrate utilization, and context-dependent metabolic flux, allowing fine-tuned functional responses to environmental cues.

This Perspective examines: (a) how metabolic shifts shape microglial function, (b) mechanistic links to mitochondrial dysfunction and inflammasome activation, (c) disease-specific evidence, and (d) translational opportunities and obstacles.

METHODS:

Because this is a narrative Perspective, we performed a targeted literature synthesis using databases including PubMed, Scopus, and Web of Science (2008–2025). Studies were selected based on relevance to microglial metabolism, mitochondrial function, inflammasome activation, and translational interventions. Priority was given to primary mechanistic studies, single-cell transcriptomic analyses, and disease-specific investigations in AD, PD, MS, and ALS. Approximately 80–120 articles were screened to ensure conceptual breadth and mechanistic depth. No formal systematic review or meta-analysis was conducted.

RESULTS:

Metabolic States Define Microglial Functional Phenotypes:

Inflammatory stimuli (LPS, aggregated proteins) rapidly increase glycolytic flux in microglia, with upregulation of hexokinase-2, PKM2, and lactate production supporting ATP and biosynthetic demands for cytokine synthesis (3,4).

Reparative/homeostatic phenotypes preferentially utilize OXPHOS and fatty-acid oxidation; however, these states are not mutually exclusive, and microglia exhibit flexible metabolic programs with overlapping glycolytic and oxidative features depending on microenvironmental demands (3).

Metabolites as Signaling Mediators:

Glycolytic enzymes have non-metabolic signaling roles (e.g., nuclear PKM2 enhances inflammatory gene transcription), and TCA intermediates such as succinate stabilize HIF-1α, thereby driving IL-1β expression, linking metabolic flux to inflammatory transcriptional programs (4,5).

Mitochondrial Dysfunction and Inflammasome Activation:

Impaired OXPHOS increases mitochondrial ROS, promotes release of mitochondrial DNA and cardiolipin, and facilitates NLRP3 inflammasome assembly, a potent amplifier of IL-1β–driven neuroinflammation (6,7,9). Chronic mitochondrial dysfunction correlates with reduced phagocytic efficiency and sustained pro-inflammatory microglial states.

Disease-specific Evidence:

Alzheimer's disease (AD): Amyloid-β exposure induces glycolytic reprogramming and mitochondrial fragmentation; single-cell studies show downregulation of OXPHOS genes in disease-associated microglia (8,9).

Parkinson's disease (PD): α-synuclein aggregates impair microglial respiration and promote inflammasome activation, contributing to dopaminergic neurodegeneration (10,11).

https://doi.org/10.63501/azz6za12

Multiple sclerosis (MS): Microglial glycolytic switching supports demyelinating inflammation, and modulation of glycolytic pathways attenuates disease severity in CNS autoimmune models (12).

Amyotrophic lateral sclerosis (ALS): Evidence from SOD1 models indicates that microglial lipid metabolic dysregulation and mitochondrial dysfunction contribute to progressive motor neuron injury. Altered lipid handling and pro-inflammatory signaling pathways, including NF-κB activation, exacerbate neurotoxicity (13).

Aging and Metabolic Priming:

Aging shifts microglial metabolism toward increased baseline glycolysis with reduced mitochondrial reserve, creating a primed state that exaggerates responses to secondary insults (14). Epigenetic regulation driven by metabolic intermediates further stabilizes pro-inflammatory phenotypes (15).

Preclinical Interventions Targeting Immunometabolism:

Glycolysis inhibitors (e.g., 2-deoxyglucose) reduce cytokine production in experimental models (3).

AMPK activators promote mitochondrial biogenesis and anti-inflammatory phenotypes (16).

NLRP3 inhibitors interrupt ROS-driven inflammatory cascades and reduce IL-1β output (6).

TREM2 signaling regulates microglial metabolic fitness, particularly lipid metabolism and mitochondrial function. Loss of TREM2 impairs ATP production and reduces microglial capacity to respond to neurodegenerative stimuli (17).

DISCUSSION:

Principal Findings and Mechanistic Synthesis:

The evidence synthesized supports a model in which microglial metabolic reprogramming is a mechanistic driver of sustained neuroinflammation. Glycolytic reprogramming supports rapid energy production and engages metabolite-driven transcriptional circuits (PKM2, succinate→HIF-1α) that perpetuate inflammatory signaling (4,5). Concurrent mitochondrial dysfunction produces ROS and mitochondrial DAMPs (damage-associated molecular patterns), activating the NLRP3 inflammasome and reinforcing IL-1β–dependent neurotoxicity (6,7,9).

Disease Relevance and Translational Implications:

Evidence across AD, PD, MS, and ALS demonstrates convergence on metabolic dysfunction as a shared pathogenic axis. Age-associated metabolic remodeling further amplifies microglial responsiveness. Therapeutic strategies should aim to recalibrate metabolism, selectively modulating metabolic pathways to restore homeostatic microglial function while limiting pathological inflammation.

Sex-dependent Variability in Microglial Metabolism:

Microglial immunometabolism exhibits sex-dependent differences, including variations in baseline metabolic activity, glycolytic responsiveness, and inflammasome activation thresholds. These differences may contribute to sex disparities in neurodegenerative disease susceptibility and progression, underscoring the need to incorporate sex as a biological variable in translational research.

Challenges and Translational Gaps:

Despite strong preclinical evidence, clinical translation remains limited. Barriers include inadequate blood–brain barrier penetration, lack of microglia-specific targeting, disease-stage heterogeneity, and potential systemic metabolic

effects. Addressing these challenges is critical for therapeutic advancement.

Roadmap for Translation:

1. Integrate longitudinal metabolomics and single-cell transcriptomics in cohort studies.
2. Validate PET and fluid biomarkers that reflect microglial metabolic states.
3. Develop microglia-targeted small molecules or delivery systems (e.g., nanoparticle carriers) that preferentially modulate microglial metabolism.
4. Conduct biomarker-enriched early-phase clinical trials with adaptive designs to assess target engagement and functional outcomes.

CONCLUSION:

Microglial metabolic reprogramming links bioenergetics to inflammatory phenotype and functional competence. Targeting immunometabolism to restore mitochondrial function, moderate pathological glycolysis, and interrupt inflammasome activation offers a compelling strategy to modify disease trajectories across multiple neurodegenerative disorders. Translational progress will require cell-selective tools, validated sbiomarkers, and careful stage-specific clinical trial designs.

AI Use Statement:

Artificial intelligence tools were used for language refinement and structural editing. No AI tools were used for data generation, analysis, or interpretation.

Conflict of Interest: None declared.

Ethical Statement: Not applicable.

Funding: None.

REFERENCES

1. Cherry, J. D., Olschowka, J. A., & O'Banion, M. K. (2014). Neuroinflammation and M2 microglia: The good, the bad, and the inflamed. *Journal of Neuroinflammation, 11*(1), 98. https://doi.org/10.1186/1742-2094-11-98
2. Ransohoff, R. M. (2016). A polarizing question: Do M1 and M2 microglia exist? *Nature Neuroscience, 19*(8), 987–991. https://doi.org/10.1038/nn.4338
3. Orihuela, R., McPherson, C. A., & Harry, G. J. (2016). Microglial M1/M2 polarization and metabolic states. *British Journal of Pharmacology, 173*(4), 649–665. https://doi.org/10.1111/bph.13139
4. Palsson-McDermott, E. M., & O'Neill, L. A. J. (2013). The Warburg effect then and now: From cancer to inflammatory diseases. *BioEssays, 35*(11), 965–973. https://doi.org/10.1002/bies.201300084
5. Tannahill, G. Á., Curtis, A. M., Adamik, J., Palsson-McDermott, E. M., McGettrick, A. F., Goel, G., Frezza, C., Bernard, N. J., Kelly, B., Foley, N. H., Zheng, L., & O'Neill, L. A. J. (2013). Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature, 496*(7444), 238–242. https://doi.org/10.1038/nature11986
6. Zhou, R., Yazdi, A. S., Menu, P., & Tschopp, J. (2011). A role for mitochondria in NLRP3 inflammasome activation. *Nature, 469*(7329), 221–225. https://doi.org/10.1038/nature09663
7. West, A. P., & Shadel, G. S. (2017). Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nature Reviews Immunology, 17*(6), 363–375. https://doi.org/10.1038/nri.2017.21
8. Li, Y., Xia, X., Wang, Y., & Zheng, J. C. (2022). Mitochondrial dysfunction in microglia: A novel perspective for pathogenesis of Alzheimer's disease. *Journal of Neuroinflammation, 19*(1), 248. https://doi.org/10.1186/s12974-022-02613-9
9. 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., Itzkovitz, S., Colonna, M., Schwartz, M.,

& Amit, I. (2017). A unique microglia type associated with restricting the development of Alzheimer's disease. *Cell, 169*(7), 1276–1290.e17. https://doi.org/10.1016/j.cell.2017.05.018

10. Subramaniam, S. R., & Federoff, H. J. (2017). Targeting Microglial Activation States as a Therapeutic Avenue in Parkinson's Disease. *Frontiers in aging neuroscience*, *9*, 176. https://doi.org/10.3389/fnagi.2017.00176
11. Mouton-Liger, F., Rosazza, T., Sepulveda-Diaz, J., Ieang, A., Hassoun, S. M., Claire, E., Mangone, G., Brice, A., Michel, P. P., Corvol, J. C., & Corti, O. (2018). Parkin deficiency modulates NLRP3 inflammasome activation by attenuating an A20-dependent negative feedback loop. *Glia*, *66*(8), 1736–1751. https://doi.org/10.1002/glia.23337
12. Everts, B., Amiel, E., Huang, S. C., Smith, A. M., Chang, C. H., Lam, W. Y., Redmann, V., Freitas, T. C., Blagih, J., van der Windt, G. J., Artyomov, M. N., Jones, R. G., Pearce, E. L., & Pearce, E. J. (2014). TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. *Nature Immunology*, *15*(4), 323–332. https://doi.org/10.1038/ni.2833
13. Zhao, W., Beers, D. R., Bell, S., Wang, J., Wen, S., Baloh, R. H., & Appel, S. H. (2015). TDP-43 activates microglia through NF-κB and NLRP3 inflammasome. *Experimental Neurology*, *273*, 24–35. https://doi.org/10.1016/j.expneurol.2015.07.019
14. Spittau, B. (2017). Aging microglia—Phenotypes, functions, and implications for age-related neurodegenerative diseases. *Frontiers in Aging Neuroscience, 9*, 194. https://doi.org/10.3389/fnagi.2017.00194
15. Gauthier, T., & Chen, W. (2022). Modulation of macrophage immunometabolism: A new approach to fight infections. *Frontiers in Immunology, 13*, 780839. https://doi.org/10.3389/fimmu.2022.780839
16. Sag, D., Carling, D., Stout, R. D., & Suttles, J. (2008). Adenosine 5′-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype. *Journal of Immunology, 181*(12), 8633–8641. https://doi.org/10.4049/jimmunol.181.12.8633
17. Ulland, T. K., Song, W. M., Huang, S. C., Ulrich, J. D., Sergushichev, A., Beatty, W. L., Loboda, A. A., Zhou, Y., Cairns, N. J., Kambal, A., Loginicheva, E., Gilfillan, S., Cella, M., Virgin, H. W., Unanue, E. R., Wang, Y., Artyomov, M. N., Holtzman, D. M., & Colonna, M. (2017). TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell, 170*(4), 649–663.e13. https://doi.org/10.1016/j.cell.2017.07.023