Why are Immune-Metabolic Pathways promising targets in Brain Disorders?

Immune–metabolic pathways are promising targets because they *sit at the core* of how brain immune cells drive, sustain, and resolve neuroinflammation across many brain disorders.

How Immunometabolism Drives Brain Disease

Microglial phenotypes are metabolically wired

- Pro-inflammatory, neurotoxic (often “M1-like”) microglia rely on **glycolysis**, while anti-inflammatory, resolving (“M2-like”) states favor **oxidative phosphorylation and fatty-acid oxidation (OXPHOS/FAO)**. (Shokr, 2025; Devanney et al., 2020)- Similar switches between glycolysis and FAO/OXPHOS are linked to microglial states in depression and affective disorders, tying **metabolic re-programming** to symptom severity. (Culmsee et al., 2019; Wang et al., 2025)**Central “metabolic sensors” control inflammation**
- Pathways such as **AMPK, mTOR, and HIF-1α** oversee these shifts in response to AD, Parkinson’s disease, multiple sclerosis, stroke, and TBI. (Shokr, 2025; Devanney et al., 2020)- Mitochondrial dysfunction and redox imbalance in microglia and peripheral myeloid cells enhance cytokine production and neuroinflammation in depression. (Culmsee et al., 2019; Rahimpour et al., 2024)## Why These Pathways Are Attractive Drug Targets

Nodal control over both metabolism and immunity

- Immunometabolic pathways act as **“checkpoints”** connecting nutrient use to cytokine output and phagocytosis, so modulating them can rebalance neuroinflammation rather than just suppressing it. (Rana et al., 2025; Guan et al., 2026)- Microglial immunometabolism is now linked to **disease progression** in AD and other neurodegenerative diseases, implying that targeting it could be disease-modifying, not just symptom-relieving. (Jung et al., 2025; Rahimpour et al., 2024)**Broad relevance across many brain disorders**
- Immunometabolic dysregulation is described in **AD, Parkinson’s, MS, stroke, TBI, spinal cord injury, depression, and neurodevelopmental disorders**, giving these pathways high “return on investment” as shared targets. (Rahimpour et al., 2024; Devanney et al., 2020; Rahimian et al., 2022)## Emerging Therapeutic Opportunities

Target/strategy	Rationale in brain disorders	Papers
Shift microglia from glycolytic M1 to OXPHOS/FAO M2	Reduce neurotoxic cytokines, enhance debris clearance and repair	(Shokr, 2025; Devanney et al., 2020)
Target lipid metabolism (e.g., TREM2, ACAT1)	Correct lipid-driven microglial dysfunction and neuroinflammation in NDDs	(Sun et al., 2025; Jung et al., 2025)
Modulate metabolic checkpoints (AMPK, mTOR, HIF-1α)	Central control of microglial activation and cytokine production	(Shokr, 2025; Kim & Lee, 2024)

FIGURE 1 How immunometabolic targets enable neuroprotection

Summary

Immune–metabolic pathways in microglia and other brain immune cells are promising targets because they mechanistically link energy use to inflammatory behavior, are dysregulated across many CNS diseases, and sit at regulatory “hubs” (AMPK, mTOR, HIF-1α, lipid pathways) that can be pharmacologically tuned. Targeting these pathways offers the prospect of truly modifying disease by restoring healthier immune phenotypes and slowing neurodegeneration, rather than only blocking single cytokines or symptoms.

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