**Background and aims:** Aberrant microglial metabolism is linked to pro-inflammatory responses, a critical pathological factor influencing stroke prognosis. Our prior single-cell RNA-sequencing and spatial transcriptomics analyses identified two stroke-associated microglial subclusters—ischemic core-associated (ICAM) and penumbra-associated (IPAM)—with opposing branched-chain amino acid (BCAA) catabolism patterns. This study investigates the role of microglial BCAA catabolism in ischemic responses and injury.
**Methods:** BCAA catabolic gene expression was quantified in vitro and in vivo. Spatial metabolomics was performed in mice after middle cerebral artery occlusion (MCAO). Conditional microglial BCAA catabolism enhancement was evaluated for infarct volume, neurological deficits, cytokines, and ICAM/IPAM proportions. Pharmacological enhancement was assessed by transcriptomics, targeted metabolomics, and Seahorse assays. Arid3a regulation was investigated using RT-qPCR, CUT&RUN, dual-luciferase assays, and metabolomics. Microglia-specific Arid3a knockdown or overexpression in MCAO mice was examined for BCAA accumulation, cytokines, subcluster shifts, infarct size, and neurological outcomes.
**Results:** BCAA catabolic genes were downregulated in ICAM but upregulated in IPAM, with marked BCAA accumulation in the ischemic core post-MCAO. Enhancing microglial BCAA catabolism alleviated neuroinflammation, promoted IPAM dominance, suppressed ICAM, and mitigated acute ischemic injury. Pharmacological enhancement inhibited glycolysis and the TCA cycle. Arid3a emerged as an upstream regulator of microglial BCAA catabolism post-ischemia. Microglia-specific Arid3a knockdown impaired BCAA breakdown, worsened infarction and deficits, and decreased neuroprotective IPAM. Conversely, Arid3a overexpression conferred acute-stage protection.
**Conclusions:** Defective microglial BCAA catabolism promotes ICAM dominance, impedes IPAM induction, and amplifies pro-inflammatory responses in ischemic stroke. Arid3a, as a critical upstream regulator, is a promising therapeutic target for mitigating microglia-mediated brain injury.
**Conflict of interest:** nothing to disclose

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## *MICROGLIAL CATABOLIC DEFECT OF BRANCHED-CHAIN AMINO ACIDS PROMOTES POST-STROKE NEUROINFLAMMATION AND ACUTE ISCHEMIC BRAIN INJURY*

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