Conditional METTL3 loss in microglia inhibits LPS-induced neuroinflammation

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Microglial activation and neuroinflammation play a critical role in the pathogenesis of Alzheimer's disease (AD). N6-methyladenosine (m6A) is the most common modification in eukaryotic mRNA, which influences numerous aspects of RNA metabolism. Recently, we found increased m6A RNA modification in microglia in AD brain. It would be of significance to understand whether and how m6A modification in microglia is involved in neuroinflammation and AD pathogenesis. In this study, we found microglial m6A modification along with the major m6A methyltransferase METTL3 is increased by LPS treatment in microglia. Increased m6A modification enhances, while decreased m6A inhibits, LPS-induced proinflammatory responses in BV2 cells. Tamoxifen-induced conditional METTL3 reduction in microglia significantly reduces the m6A modification in the mouse brain without affecting microglial morphology, cell number and mouse brain size. However, LPS-induced microglial activation is apparently rescued by conditional METTL3 loss. Similarly, LPS-induced proinflammatory responses is significantly inhibited by conditional loss of METTL3 in microglia. In addition, A1-specific astrocytic genes expression by RNA-seq is significantly induced by LPS-induced neuroinflammation in mice, and it could be rescued by conditional loss of METTL3 in microglia. Taken together, our data indicate that METTL3-dependent m6A elevation in microglia regulates neuroinflammatory gene expression and mediates microglial activation, which could contribute to microglial dysfunctions and neuroinflammation in AD.

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