Dysregulated microRNAs in amyotrophic lateral sclerosis microglia modulate genes linked to neuroinflammation

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MicroRNAs (miRNAs) regulate gene expression at post-transcriptional level and are key modulators of immune system, whose dysfunction contributes to the progression of neuroinflammatory diseaseas such as amyotrophic lateral sclerosis (ALS), the most widespread motor neuron disorder. ALS is a non-cell-autonomous disease targeting motor neurons and neighboring glia, with microgliosis directly contributing to neurodegeneration. As limited information exists on miRNAs dysregulations in ALS, we examined this topic in primary microglia from superoxide dismutase 1-G93A mouse model. We compared miRNAs transcriptional profiling of non-transgenic and ALS microglia in resting conditions and after inflammatory activation by P2X7 receptor agonist. We identified upregulation of selected immune-enriched miRNAs, recognizing miR-22, miR-155, miR-125b and miR-146b among the most highly modulated. We proved that miR-365 and miR-125b interfere, respectively, with the interleukin-6 and STAT3 pathway determining increased tumor necrosis factor alpha (TNFα) transcription. As TNFα directly upregulated miR-125b, and inhibitors of miR-365/miR-125b reduced TNFα transcription, we recognized the induction of miR-365 and miR-125b as a vicious gateway culminating in abnormal TNFα release. These results strengthen the impact of miRNAs in modulating inflammatory genes linked to ALS and identify specific miRNAs as pathogenetic mechanisms in the disease.

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Abbreviations: ALS, amyotrophic lateral sclerosis; nt, non-transgenic; SOD1, superoxide dismutase; miRNA, microRNA; TNFα, tumor necrosis factor alpha; QPCR, quantitative RT-PCR; IL-6, interleukin-6; UTR, untraslated region; (BzATP), 2′(3′)-O-(4-Benzoylbenzoyl)adenosine 5′-triphosphate; NF-κB, nuclear factor kappa B

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