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DUAL AND OPPOSING ROLES OF MIR-124 IN EPILEPTOGENESIS ARE MEDIATED THROUGH NRSF AND INFLAMMATORY PATHWAYS

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Insult-provoked transformation of neuronal networks into epileptic ones involves multiple mechanisms. Intervention studies have identified both dysregulated inflammatory pathways and NRSF-mediated repression of crucial neuronal genes as contributors to epileptogenesis. However, it remains unclear how epilepsy-provoking insults (e.g., prolonged seizures) induce both inflammation and NRSF and whether common mechanisms exist. We examined miR-124 as a candidate dual regulator of NRSF and inflammatory pathways. Status epilepticus (SE) induced by

kainic acid led to reduced miR-124 expression via SIRT1 – and, in turn, miR-124 repression – via C/EBP α upregulated NRSF. We tested whether augmenting miR-124 using miR-124 mimics/agomirs after SE would abort epileptogenesis by preventing both inflammation and NRSF upregulation. SE-sustaining animals developed epilepsy as detected by 24-video EEG monitoring, but supplementing miR-124 did not modify epileptogenesis. Examining this result further, we found that synthetic miR-124 not only effectively blocked NRSF upregulation and rescued NRSF target genes, but also augmented microglia activation and inflammatory cytokines. Thus, miR-124 attenuates epileptogenesis via NRSF while promoting epilepsy via inflammation.