Brain Injury Signaling Events Alter Expression of Mitochondria Associated microRNA

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Mitochondria serve as the powerhouse of cells, respond to cellular demands and stressors, and play an essential role in cell signaling, differentiation, and survival. There is clear evidence of compromised mitochondrial function following traumatic brain injury (TBI), however, the pathological consequences are not well known. MiRNA are small non-coding RNA molecules that regulate post-transcriptional gene expression, and serve as important mediators of neuronal development, synaptic plasticity, and neurodegeneration. Our recent studies suggest that mitochondria may serve as regulators of cellular miRNA expression following TBI. Here, we extend our initial observations by reporting the effect of TBI related secondary injury events on mitochondria associated miRNA expression. Synaptic and non-synaptic mitochondria were isolated from naïve adult rat cortex and exposed to concentrations of Ca2+ that inhibit State III mitochondrial respiration by 15-30%. RT-qPCR analysis demonstrated that Ca2+ treatment significantly decreased miR-150 and miR-146a levels in synaptic, but not non-synaptic mitochondria. This observation is particularly intriguing for two reasons. First, synaptic and non- synaptic mitochondria exhibit differential sensitivities to Ca2+ and respond differently to TBI over time. Second, the levels of miR-150 and miR-146a have been shown to decrease in mitochondria isolated from the hippocampal formation following TBI. In a separate set of experiments, rat primary cortical astrocytes were treated with various concentrations of glutamate followed by mitochondrial isolation and single tube RT-qPCR measurement of select miRNA. These studies revealed that mitochondria levels of miR-146a and miR-150 significantly decreased while levels of these same miRNAs were unchanged in cytoplasmic fractions. Taken together, we hypothesize that TBI-related secondary injury events, such as high Ca2+ and exposure to excitotoxic levels of glutamate, lead to altered expression levels of certain mitochondria-associated miRNAs in a manner similar to that observed following TBI.

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