Effects of Traumatic Brain Injury on miRNA Association with Mitochondria and Intervention Using a Novel Peptide-based Nanoparticle Delivery S

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Traumatic brain injury (TBI) is a leading cause of long-term impairments in higher cognitive function. Ongoing destructive secondary injury events occur minutes to days after the initial insult characterized by a cascade of pervasive biochemical and pathophysiological stressors, including glutamate excitotoxicity, mitochondrial dysfunction, free radical-mediated oxidative damage, inflammation and activation of necrotic and apoptotic cell death signaling pathways. A rapid and sustained phase of mitochondrial dysfunction after TBI impacts a number of important cellular events. We demonstrated previously that specific hippocampal mitochondria-associated microRNAs (miRNAs) are altered following a controlled cortical impact (CCI) injury in rats. Our new studies reveal that the levels of several mitochondria-associated miRNAs (e.g.miR-142-3p, miR-142-5p, miR-146a, miR-155 and miR-223) are altered early on (3-24 hr), but start to normalize by 72 hr after TBI. Knowledge of the temporal changes in mitochondria associated miRNA levels after TBI provides an opportunity to target specific miRNA at specific time points. We have previously shown that miR-107 is significantly downregulated in hippocampal neurons at 24 hr following TBI. In the present study, we used a 21 amino acid peptide-based nanoparticle approach to test whether delivery of miR-107 mimic alters hippocampal levels of miR-107 and two miR-107 validated targets, granulin and beta secretase 1 (BACE1). At 48 hr following stereotaxic injections of 10-20 pmole of peptide+miR-107 into the dorsal hippocampus, miR-107 activity increased by 150% while granulin/BACE1 mRNA levels were downregulated by 20-40% depending upon the peptide+miR-107 ratio/concentration. The outcomes of this study suggest a temporally dynamic interaction of miRNA with mitochondria that is dependent, in part, on mitochondrial bioenergetics, and suggest a potential role for mitochondria in dictating miRNAs' cellular function. The study also demonstrates the use a peptide-based nanoparticle approach to effectively deliver miRNA mimics or inhibitors as a way to target specific miRNA activities following TBI.