Transcriptomics identifies genes and signaling pathways that may regulate neurodegeneration

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Neuronal death is a normal feature of brain development but also a defining feature of neurodegenerative diseases when improperly regulated. Results of a detailed and comprehensive analysis of transcriptome expression alterations during neuronal death have been reported. A large number of genes previously not linked to neuronal death were identified in the study. Although further functional analyses are needed, some of these genes may be important players in the regulation of neuronal death and represent potential targets for the development of novel therapies.

Massive elimination of neurons is a critical aspect of normal nervous system development but also represents a defining feature of neurodegenerative pathologies, such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Although the molecular events that trigger neuronal death in each of these neurodegenerative diseases is distinct, the downstream apoptotic process through which neurons die in these pathologies are thought to share commonalities to each other, as well as to developmentally-regulated neuronal death. Identifying genes that promote or prevent neuronal death would thus be an important step in understanding both developmentally-regulated neuronal death as well as the mechanisms underlying degenerative brain disorders. Scientists at Southern Methodist University, led by Professor and Chair of Biological Sciences Santosh D'Mello, have used RNA-Seq to conduct transcriptome profiling of gene

expression changes in dying neurons.

This study, reported in the February 2015 issue of *Experimental Biology and Medicine*, utilized cultured cerebellar granule neurons, one of the most widely used models to study neuronal death. Other labs have used DNA microarray analysis to characterize gene expression changes in this model. However, microarray analysis is only capable of measuring the status of known transcripts, and expression of low-abundance mRNAs is often not detected by the hybridization-based approach. While changes in the expression of several hundred genes were detected by microarray analyses, in the study by D'Mello and colleagues over 4,000 genes displayed significantly altered expression. Most affected were genes functioning in cell death and survival regulation, cell growth and proliferation and molecular transport. A large number of genes involved in nervous system development and function were also deregulated.

Analysis of signaling pathways that were affected pointed to changes in mitochondrial function and oxidative phosphorylation, consistent with a number of studies showing perturbations of these pathways in neurodegenerative disorders. A large number of genes previously not linked to developmentally-regulated neuronal death or neurodegenerative pathologies were identified. "This is a first step in the identification of novel but important players regulating neuronal survival and death" said Dr. D'Mello. "Future studies will determine to what extent the novel genes identified in our study are involved in regulating neuronal death, including death associated with neurodegenerative disease."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "D'Mello and colleagues have performed a transcriptomic study, utilizing RNA-Seq, to identify transcripts that are changed in expression in dying neurons. Utilizing this very sensitive technique they were able to demonstrate significant changes in the expression of over 4000 genes. This study opens the door to future studies on which of

these many genes are functionally involved in normal neuronal death and that associated with various neurodegenerative disorders.

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