Spatial Transcriptomics Demonstrates Tissue-Specific Differential Gene Expression in a Mouse Model of Spinal Muscular Atrophy

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Background: Spinal muscular atrophy (SMA) is an autosomal recessive disease resulting from insufficient survival motor neuron (SMN) protein that afflicts ~1 in 10,000 births. Motoneurons are specifically sensitive to low SMN levels and motoneuron death is the hallmark of SMA. We investigated how low SMN levels affect the gene expression profile in multiple tissue types at an early symptomatic disease state.

Methods: Spatial transcriptomic data using the Visium platform, collected from lumbar spinal column sections at postnatal day 4 from female normal and severe SMA mice (n=4 each), were analyzed. Systematic literature review identified tissue-specific biomarkers, which were compared to biomarkers calculated from graph-based clustering and compared to microanatomy using Loupe Browser. Clustering and differential gene expression analysis were performed in Partek Flow.

Results: Clusters were annotated using biomarker expression patterns. Significant gene expression changes across thirteen tissue types were observed at this early disease state. For example, muscles clustered into type 1, type 2b, and tendon-associated and were significantly affected in SMA mice. Several transcripts associated with muscle atrophy were increased in SMA while hypertrophy mRNAs were unchanged. Interestingly, genes associated with bone resorption and osteoporosis were overexpressed in SMA bone, which may be important as clinical studies show decreased bone density and frequent fractures in children with SMA. Preliminary clustering of ST data from neuronal subtypes and other cells within the spinal cord reveal transcriptional changes in SMA mice.

Conclusion: These data demonstrate that low SMN protein levels are associated with extensive tissue-specific gene expression changes early during disease progression. This implies that SMN deficiency may progress to involve multiple organ systems as children treated for SMA live longer. Validation of identified key genes will contribute to understanding of SMA pathogenesis and offer insights for novel treatments to improve outcomes in all stages of SMA.