Transcriptional Correlation Analysis of Livers Undergoing Normothermic Machine Perfusion Links Gene Expression Patterns with Graft Functional Metrics

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Introduction: Normothermic machine perfusion (NMP) allows dynamic organ preservation under physiological conditions and facilitates real-time assessment of graft viability for transplant. The aim of this study was to delineate transcriptional patterns that correlate with liver functional metrics during NMP.

Methods: Ten discarded human livers, rejected by all regional transplant centers, were obtained from donation after circulatory death (DCD). The livers underwent 12 hours of NMP with oxygenated red blood cells. Serial tissue and plasma samples were collected. Perfusate lactate clearance <2.5 mmol/L was used to denote livers with adequate hepatocellular function. Transcriptome sequencing was performed on serial biopsies taken at 0 (pre-perfusion), 3, and 6hr of NMP. Weighted gene co-expression network analysis (WGCNA) was performed to correlate each gene set module with functional metrics measured during NMP. Functional enrichment analysis was performed on modules of interest.

Results: Expression data at 0, 3 and 6 hours of NMP was used to construct the weighted co-expression network. The WGCNA package was then used to correlate each gene set module with various liver demographics and functional data collected during NMP. Genes from the module with the highest correlation value with lactate clearance were further analyzed. Functional enrichment of this module revealed biological processes related to cellular metabolism, biosynthesis, cell death, and autophagy. These genes were found to be more highly expressed in livers with adequate hepatocellular function compared to those with inadequate function. In addition, this gene co-expression module was significantly correlated with other traits including steatosis, age, sex and cold ischemic time indicating a functional relationship with these factors.

Conclusion: WGCNA leverages the wide variability in human liver tissues to facilitate identification of gene expression patterns with specific liver characteristics (such as donor age and cold ischemic time) and measurable functional metrics during NMP (lactate clearance, vascular resistance). Understanding these correlations will be critical to designing targeted therapeutics for rehabilitation of discarded or high-risk livers during NMP.