

A080 Harnessing the Fetal Hepatocyte Proliferative Phenotype to Improve Liver Cell Transplantation

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Introduction: Chronic Liver Disease (CLD) is a leading cause of death in the US, and orthotopic liver transplantation is restricted by the limited availability of viable donor organs. A barrier to using hepatic cell transplantation (HCT) as an alternative therapy is the short duration of efficacy of transplanted adult cells. Fetal hepatocytes have shown durable long-term potency in clinical trials, but ethical concerns prevent their procurement. We believe that comparing the histone post-translational modification (hPTM) profiles of transplanted fetal hepatocytes to surrounding adult host tissue will elucidate gene regulation mechanisms responsible for the fetal proliferative phenotype. **Methods:** Using the Dipeptidyl Peptidase IV rat model, we performed LCM on sections of liver 10 months following fetal HCT. We collected paired fetal- and adult-origin hepatocytes from 5 biological replicates. These samples were submitted for hPTM analysis by the Northwestern University Proteomics Center of Excellence and for RNA-Seq by GENEWIZ. Results were analyzed in R. **Results:** A total of 92 histone marks were quantitated, of which 50 showed a significant difference in average relative abundance between our fetal and adult samples ($q < 0.05$). The results for the significantly-different marks were compared to our previous hPTM MS studies using fetal/adult liver sections, as well as immunopurified pre-transplant fetal/adult hepatocytes. Multiple hPTMs were found to have significant regulation differences in fetal colonies in the same direction as both fetal liver and fetal hepatocytes, including H3K27 me2 and me3. **Conclusions:** This study demonstrates that fetal hPTM characteristics persist in transplanted cells for at least 10 months following HCT, and likely confer expression differences to genes driving proliferation. We detected a consistently lower abundance of di/trimethylation of H3K27 in fetal cells across all studies, which have known roles in repression of transcription in developing cells. Lower abundance of these hPTMs suggest that fetal hepatocytes could retain progenitor-cell-like gene expression patterns which encourage proliferation. As part of a multiomics approach, we aim to synthesize our hPTM results with RNA-Seq to identify critical regulatory mechanisms linked to proliferation-driving gene expression, which can be exploited to reprogram adult or induced hepatocyte-like cells into a phenotype more favorable for HCT.