Diabetic Complications Consortium

Application Title: Multi-scale imaging tools to map pathology and gene expression in the human kidney

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1. Project Accomplishments:

We have developed tools to evaluate the level of intra-kidney heterogeneity in pathology and gene expression in the context of the intact human kidney. We have performed stereotactic biopsy in over 40 kidneys donated to research (not accepted for transplantation), from both healthy and diabetic donors. We first evaluated the level of spatial heterogeneity in pathology measured from biopsy. We applied and tested stereotactic biopsy as a tool to link kidney microstructure and gene expression to whole-organ anatomy

2. Specific Aims:

Aim 1: Measure heterogeneity in tissue pathology using MRI and site-directed stereotactic biopsy in the healthy and diabetic human kidney.

Results: We systematically biopsied >40 human kidneys three times each from three different locations. A blinded, board- certified pathologist scored the biopsy tissues and we evaluated the levels of glomerulosclerosis and fibrosis (IFTA) detected from each kidney. Histopatholgy scores varied widely across biopsies from the same kidney, over 100% in some cases. The most consistent scoring occurred when the biopsies were acquired from the lower pole of the kidney. These findings were true regardless of kidney donor profile index (KDPI), and was independent of sex or diabetic status. Through our analysis we found several key features that, for the first time, that a biopsy may be effective in detecting pathology in a specific cohort of patients, namely those without hypertension. In this case, both IFTA and glomerulosclerosis scores were very reliable (<10% error) indicators of whole kidney pathology. We also found that histopathologic scores from biopsy were only reliable when they contained >10 glomeruli. We conclude that there is a high level of heterogeneity in pathology in the human kidney that is likely mirrored in spatially variable patterns in gene expression. This work has enabled systematic investigations of these patterns, which are the focus of ongoing work. This work has also revealed circumstances in which biopsy can be recommended for evaluation of kidney health.

Aim 2: Map gene expression across the kidney and correlate transcriptomics with tissue microstructure from MRI.

We have collected samples across the human kidney to measure variability in gene expression and its relationship to spatially- coincident pathology. Our findings of high levels of heterogeneity led us to focus this work on developing the techniques to systematically extract tissue from anatomical regions of the kidney, aimed at facilitating

studies of gene expression related to the histopathologic variability. Manuscript is in preparation.

3. Publications:

Publications pending.