The Cellular Pathology of Early Kidney Disease

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Background: Deaths due to chronic kidney disease have doubled since 1990, in large part due to the global epidemic of type 2 diabetes, and a limited understanding of the underlying cellular pathological processes hampers the development of effective targeted renal therapies. Cell transcriptomic (scRNA-seq) studies in human kidney tissue are beginning to highlight cell specific differences in renal diseases, including diabetic nephropathy (DKD). However, renal damage is often asymptomatic until 85% of renal clearance is lost, and so it is proving difficult to distinguish between the dysregulated pathways driving renal damage and later tissue responses to injury. Moreover, comparisons between human disease tissue and healthy controls are confounded by genetic and environmental heterogeneity, and there is a need to correlate transcriptomic insights with spatial cellular relationships at the protein level in order to understand cellular cross-talk in context.

Over 200 kidney transplants are performed in the Oxford Transplant Unit each year, including in patients with a known risk of disease recurrence in the donor kidney post transplantation. These conditions include IgA nephropathy, some forms of focal segmental glomerulosclerosis (FSGS) and systemic diseases, of which DKD is the most common, affecting over 40% of patients on the transplant waiting list. FSGS recurs in 25% of cases, sometimes within hours or days post transplantation, DKD recurs histologically within 2 years, while IgA recurs in over 50% of patients by 4 years post-transplant. Access to paired pre- and post-implantation transplant kidney biopsy samples presents a unique opportunity to study the very earliest pre-clinical stages of active renal disease in previously normal kidneys.

Hypothesis: The cellular transcriptomic and proteomic signatures in early renal disease recurrence will identify disease specific modulators and novel therapeutic targets.

Aims: We will use the cellular transcriptomic and proteomic signatures of early renal disease to:

• Identify candidate novel causative pathways for renal disease, including interactions between glomerular cells and infiltrating immune cells, proteins or small molecules.

• Develop multiplex imaging panels applicable to larger biopsy tissue datasets, addressing heterogeneity and with potential as a tool to increase power in clinical trials.

• Illuminate early modulators of renal disease with potential as drug targets

Description of Work: Through the Oxford Transplant Biobank (led by Prof Rutger Ploeg, NDS) we have access to pre-implantation renal tissue from all living donors in Oxford, and 90% of all UK
kidney donors via the QUOD biobank, with ethical approval to seek consent for a research biopsy post transplantation.

1. **We will recruit 20 transplant patients in Oxford** with biopsy proven native kidney disease due to DKD, IgA or MPGN. Matched pre-implantation tissue from healthy donors will act as controls. For FSGS, we will recruit patients undergoing work up for living donor transplantation and obtain paired pre and post implantation samples. Routine clinical histology (Prof Ian Roberts, Renal Histopathologist) will define recurrence and exclude rejection or pre-implantation disease. **On each paired sample, we will perform:**
   a) Renal cortex spatial **scRNA-seq** (10x + BGI), comparing pre-implantation healthy donor tissue to samples post-transplantation with alignment to conventional morphology (Prof Jens Rittscher). Comparisons across the disease states and in those with and without histological disease recurrence will be used to adjust for immunosuppression (Dr Katherine Bull).
   b) **aCellular podocyte and glomerular proteomics** using laser capture micro-dissection and mass spectrometry of over 4000 proteins (with Dr Roman Fischer, TDI).
   c) **Multiplex Imaging.** Combined dataset analysis will inform the design of disease specific high throughput 40+ marker panels for tissue imaging (Hyperion-iCytof, Nanostring or CellDive).

2. **Disease associated signatures will be validated in further renal samples** including existing biobank tissue, to identify potential drug targets and early biomarkers of recurrence or treatment response.

**Supervisor’s recent relevant publications:**