M02: Assessment of 'molecular organ age' in retrieval kidney biopsies

Dr Roy Zhang[1], Dr Patrick Trotter[1], Dr James McCaffrey[1,2], Dr Benjamin Stewart[1,3], Dr John Ferdinand[1], Dr Kevin Loudon[1], Dr Alexandra Riding[1], Dr Jonathan West[1], Dr Ashley Ferro[1], Dr Robert Kirkpatrick[4], Professor Menna Clatworthy[1,3]

[1]Molecular Immunity Unit, University of Cambridge Department of Medicine, Cambridge, United Kingdom. [2]Department of Pathology, Cambridge Universities NHS Foundation Trust, Cambridge, United Kingdom. [3]Cellular Genetics, Wellcome Sanger Institute, Hinxton, United Kingdom. [4]Glaxo-Smith-Kline, Stevenage, United Kingdom

Abstract

Introduction: Kidney transplantation is an excellent treatment for end-stage kidney failure but organ shortage remains a problem. The use of marginal donor kidneys is hampered by variable outcomes and an inability to accurately predict post-transplant function. Transcriptomic profiling enables an in-depth assessment of the dominant molecular processes occurring in kidneys, quantifying the expression of ~25,000 genes, with the potential to identify novel outcome-associated biomarkers.

Methods: Retrieval biopsies were obtained via the Quality in Organ Donation (QUOD) biobank from n=271 deceased circulatory death kidneys and processed for bulk RNA-sequencing and histological assessment. Transcriptional features associated with delayed graft function (DGF) and 12-month estimated glomerular filtration rate (eGFR) were assessed using differential gene expression and pathway enrichment. Weighted gene co-expression network analysis (WGCNA) was used to identify gene modules co-associated with outcome and age.

Results: Following adjustment for variable tissue composition, we found enrichment of neutrophil and acute inflammatory gene signatures associated with better transplant outcomes, including DGF and 12-month eGFR. In contrast, kidneys with a worse prognosis showed positive enrichment for fibrosis- and adaptive immune-gene signatures (Figure 1), with increased interstitial lymphocyte infiltration confirmed histologically. WGCNA of cortical biopsies identified an adaptive immune gene-rich module that significantly associated with increasing age and worse outcomes (Figure 2). Cellular deconvolution using human kidney reference single cell transcriptomes confirmed an increase in kidney-specific B and T cell signatures, as well as kidney macrophage, myofibroblast and fibroblast genesets in this module, corroborating our differential expression analysis and localising these findings to the cortex.

Discussion: Altogether, our work reveals the cellular molecular features of pathological organ ageing, identifiable at organ retrieval, and supports the use of transcriptomic assessment of 'molecular organ age' in pre-transplant kidney assessment.

Figure 1: Gene set enrichment analysis using signatures from the Kidney Cell Atlas.

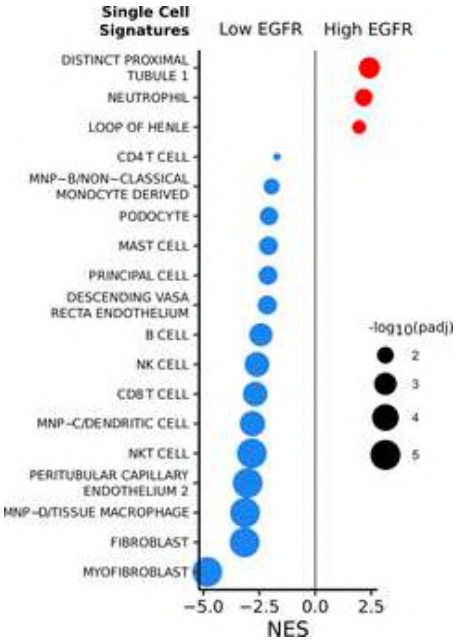
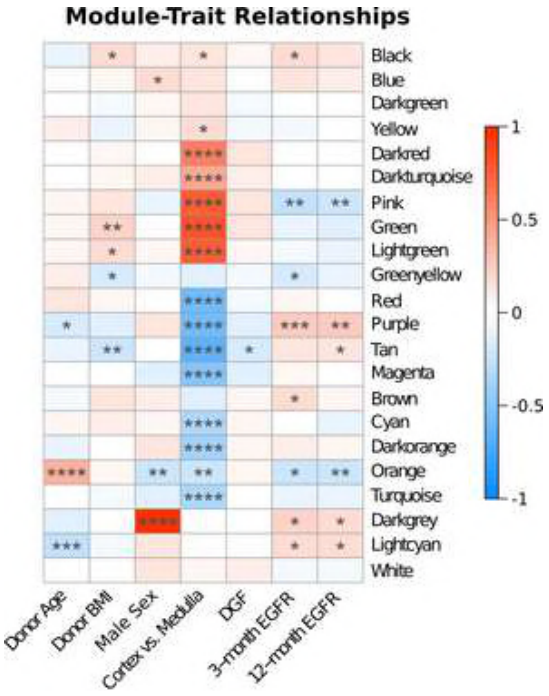


Figure 2: Module-trait relationships. Colour indicates correlation (*, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001).



Categories: Basic and translational science (as per category - all science)