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P083 -Elucidating the relationship between renal inflammation and metabolism in chronic kidney disease in the mouse through integrative computational modeling

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Background: Chronic Kidney Disease (CKD) is the progressive and irreversible loss of kidney function over time. Many patients remain asymptomatic until the advanced stages so diagnosis often comes too late for therapeutic conventional intervention. Fibrosis is the pathophysiological hallmark of progressive CKD regardless of the initial aetiology and is characterised by fibroblast activation, accumulation of extracellular matrix, vascular rarefaction and tubular atrophy. It often coexists with, or is preceded by, inflammation but what drives progressive fibrosis after resolution of inflammation is unclear. Recent evidence suggests that damaged tubular epithelial cells (TECs) drive the fibrotic process through the release of pro-inflammatory and pro-fibrotic cytokines but few studies have focused on the metabolic impact of damage in TECs and how this varies over time.
TECs have very high mitochondrial activity and rely on fatty acid oxidation for maximal ATP production. Alterations in cellular metabolism have been demonstrated in heart failure and cancer and a recent study has revealed that lipid metabolism is dysregulated in TECs following acute kidney injury (AKI).

Aim: To investigate the relationship between inflammation, fibrosis and metabolism using RNA seq and trascriptomic analysis in a mouse model of CKD following AKI.

Methods: We adopted a mouse model of aristolochic acid nephropathy (AAN) (2 S/C injections of AA, 3.5 mg/kg 5 days apart in CD1 mice) in which acute inflammation and AKI peak and resolve over 4-6 weeks, followed by progressive fibrosis and CKD over three months. We undertook transcriptomic analysis on the kidney tissue for three time points of disease progression (day 0, day 32 (AKI) and day 100 (CKD)) and compared them to age-matched controls.

Results: As expected, inflammatory gene expression was markedly increased on day 32 of AAN compared to controls. At day 100 only a subset of inflammatory genes remained elevated. By performing gene ontology enrichment analysis on differentially expressed genes we identified that the expression of pro-fibrotic pathways mirrored that of the inflammatory gene expression, peaking in the acute phase and reducing significantly by day 100, despite evidence of progressive fibrosis on histology and worsening of renal function. Conversely, many of the downregulated genes in the acute phase were associated with metabolic activity and this downregulation persisted to a similar degree at day 100. Using computational genome-scale metabolic models (GEMs) to predict the phenotypic impact of the transcriptomic data we showed the majority of central carbon metabolism (Glycolysis, TCA, Fatty acid metabolism, amino acid metabolism and oxidative phosphorylation) of the kidney was downregulated in the CKD model, whilst fatty acid biosynthesis and elongation were upregulated. We also observed that metabolic turnover in the pentose phosphate pathway was increased during CKD. After performing comprehensive correlative and clustering analysis between the inflammation and metabolic genes, we observed the inflammation response is negatively correlated with fatty acid metabolism and oxidative phosphorylation.

Conclusion: Alterations in renal cell metabolism are closely associated with inflammation but may persist after resolution of the acute injury. This insight may provide us with new therapeutic targets in managing progressive CKD in the future.