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P457 -Proximal tubule damage is sustained in acute to chronic renal injury transition and specific early therapeutic intervention can limit the subsequent chronic kidney disease.

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Introduction: Acute kidney injury (AKI) is recognized to be an early portent of chronic kidney disease (CKD). Sensitive biomarkers of AKI could be beneficial for the earlier diagnosis, identification of mechanism of injury, and assessment of site and severity of injury. N-acetyl-β-glucosaminidase (NAG) is a proximal tubule lysosomal enzyme that has been proven to be a sensitive and persistent indicator of tubular injury. Our early work demonstrated that Kirsten Ras (K-Ras) plays an important role in the activation of myofibroblasts in murine models chronic fibrosis. More recently we have observed a potential role for K-Ras in AKI leading to chronic injury.

Here, we utilise urinary NAG to help interpret an Aristolochic Acid induced acute to chronic renal injury model with a therapeutic intervention targeting K-Ras.

Methods: CD1 mice received intra-peritoneal injections of either 3.5mg/kg Aristolochic Acid (AA) or normal saline on day 1 and on day 5. Treatment groups, in addition to the injections of AA, were 1) commencement of subcutaneous injections of K-Ras ASO 2 days prior to the first AA injection; 2) commencement of subcutaneous injection of K-Ras ASO on day 20, after the acute phase of renal injury. Urine samples were stored at -80° prior to being assayed for NAG activity and creatinine using the Rapichrome™ Second Generation NAG assay. NAG activity was measured in µmol/hr/L and indexed for urinary creatinine, mMol. Statistical analysis was by Mann-Whitney and Kruskal-Wallis tests.

Results: We previously reported a biphasic increase in BUN of 4.6 fold at day 12 and 1.5 fold at day 100 and a 7 fold increase in collagen deposition at day 100 in this model. Here we observed raised NAG levels from a median of 362 (range 280- 423) to 863(673-1081) at day 30 to 943 (621-1416) at day 100 following AA administration.

In treatment group 1, ASO 143 administration initiated at day -2 before the first AA administration significantly reduced NAG at day 100 to 444 (71-1342). The effect of control oligo was not statically significant.

In treatment group 2, ASO treatment at day 20, after the peak of acute injury as determined by BUN levels, had no effect on NAG activity at day 100.

Discussion: Our results demonstrate that urinary NAG activity, as determined by an assay employing a highly sensitive VRA-GlcNAc substrate can be used in murine models to monitor AA induced tubular damage over acute to chronic transition and monitor therapeutic interventions.

In this model the early administration of K-Ras targeting ASO was followed by a sustained and significant reduction in urinary NAG. This suggests that the ASO prevents proximal tubule injury and that this specific injury is related to the degree of fibrosis and loss of renal function observed in the chronic phase.