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P166 -Growth hormone inhibition in Autosomal Dominant Polycystic Kidney Disease

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INTRODUCTION: Autosomal dominant polycystic kidney disease (ADPKD) is caused mainly due to mutations in the PKD1 gene and results in progressive enlargement of renal cysts eventually leading to end-stage renal failure. Tolvaptan is currently the only available treatment that delays disease progression, however it is contraindicated in some ADPKD patients. Thus, there is an urgent and unmet clinical need for studies that will pave the discovery of novel therapeutic targets.
The Janus Kinase and Signal Transducers and Activators of Transcription (JAK-STAT) signalling pathway has been shown to be abnormally expressed and involved in ADPKD pathogenesis. Our laboratory recently identified that serum growth hormone (GH) levels were statistically increased in an ADPKD mouse model (PKD1nl/nl), when compared to PKD1 wild-type littermates. This led to aberrant upregulation of JAK2-STAT5 signalling, in turn leading to enhanced renal epithelial cell proliferation. We have further investigated the involvement of this pathway and the impact of growth hormone inhibition in PKD models.

HYPOTHESIS: Inhibition of growth hormone signalling may lead to reduced JAK/STAT activity in turn leading to reduced cystogenesis in vitro and in vivo.

METHODS: Recombinant wild-type human growth hormone (hGH-WT) and a growth hormone antagonist (hGH-G120R) which acts a competitive growth hormone receptor inhibitor have been expressed in E.coli and purified using metal chelate affinity chromatography. Laboratory-purified GH has been tested for bioactivity against commercial GH, the ability of the antagonist to reduce GH-induced signalling was tested by immunoblotting. ADPKD-derived human renal epithelial cells (SKI001, OX161 clone 1) were used to assess the effects of inhibition of GH signalling on proliferation (PCNA staining), target gene expression (qPCR) and cystogenesis in vitro.

RESULTS: Wild-type human growth hormone and the hGH-G120R antagonist were successfully expressed in E. coli and purified using nickel chelate affinity chromatography. Their bioactivity was measured through STAT5 activation in ADPKD-derived human cells, with commercial hGH used as a positive control. Both laboratory purified and commercial hGH were able to potently enhance STAT5 activity (phospho-tyrosine STAT5) in human ADPKD-derived cells. GH-induced STAT5 activity resulted in increased proliferation of ADPKD-derived cells. Pre-treating ADPKD cells with the GH antagonist (hGH-G120R) led to reduced STAT5 activity and restored proliferation levels.

CONCLUSION: Inhibition of growth hormone signalling along the GHR-JAK2-STAT5 axis has potential as a novel therapeutic target in ADPKD.