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P167 -JAK2 inhibition halts the growth of polycystic kidney disease-derived epithelial cysts in vitro.

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BACKGROUND: Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects millions of people worldwide and currently remains without a cure. Mutations in the Polycystic Kidney Disease 1 (Pkd1) gene are responsible for the majority of ADPKD cases. Tolvaptan is the only approved drug but it is available only to some patients, moreover severe side effects preclude its use in the majority of patients, thus new therapies are urgently needed. A number of groups have reported that the Janus kinase and Signal Transducers and Activators of Transcription (JAK/STAT) pathway is abnormally activated in ADPKD and, critically, it contributes to pathogenesis. Currently 12 small molecule JAK/STAT inhibitors are in various stages of clinical trials, including three selective JAK inhibitors (Ruxolitinib, Tofacitinib and Baricitinib), which are already approved for rheumatoid arthritis and types of leukaemia.

HYPOTHESIS: Reducing JAK/STAT activity with the use of selective small molecule JAK inhibitors may reduce cystogenesis.

METHODS: To test if JAK/STAT inhibition alters cystic growth, we used human ADPKD-derived epithelial cells (SKI-001 and OX161-c1) or mouse epithelial cells with and without deletion of the Pkd1 gene (F1 Pkd1+/+ and F1 Pkd1-/-). To generate cysts, we cultured cells in basement membrane Matrigel, which allows growth of cells in three-dimensions. Cells were treated either with JAK inhibitors at concentration of 5-10μM (concentrations found in plasma of treated patients and are physiological dosages) or with equal volumes of vehicle control (i.e. DMSO). Cysts were allowed to grow for up to 12 days and cyst diameter was measured every 2 days. Immunohistochemistry was used to assess expression of JAK1 and JAK2 in kidney tissues from mice with ADPKD (Pkd1nl/nl) and wild-type littermates at 5 and 10 weeks of age.

RESULTS: Immunohistochemical examination revealed that JAK1 and JAK2 are highly expressed in ADPKD murine kidneys in vivo. Next, we reduced JAK activity with treatment with Ruxolitinib, which is a selective small molecule inhibitor of JAK1 and JAK2. Ruxolitinib significantly reduced the growth of cysts over time when compared to vehicle control. This effect was dose and time-dependent with the greatest effect seen with the highest concentration at days 4-10.

CONCLUSION: Our study suggests that JAK inhibition reduces cystogenesis in vitro.