p21 upregulation mediates cyst progression in mouse models of Polycystic Kidney Disease

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Polycystic Kidney Disease (PKD) is an inherited disease affecting 1:500 – 1:1000 people worldwide and the mechanism behind cystogenesis remains unclear. Recent data have indicated an upregulation of the cyclin-dependent kinase inhibitor p21/wif1/cip1 in murine models of PKD. Previous studies concluded that p21 expression increases following PC1/PC2 overexpression. Expression of p21 is normally linked to cell cycle arrest or senescence. As PKD is characterized as a hyperproliferative disease, the upregulation of p21 led to my hypothesis that p21 is functioning as an inhibitor of cell proliferation controlling the rate of cyst expansion.

To investigate this, I am using a conditional *Pkd2* knockout mouse model to determine p21 expression and cell proliferation (anti-ki67 staining) during the initial stage of renal cystogenesis using immunofluorescence. This will allow me to determine if p21 is expressed in proliferating cells (ki67+), a sign of cell cycle arrest possibly due to cell damage, or non-proliferating cells (ki67-) which would indicate senescence. These data will allow me to correlate p21 expression and proliferation to cyst initiation and expansion.

My results do not show an increase in proliferation during cyst initiation based on ki67 expression, however, p21 expression is increased which reveals a proliferation-independent function of p21 in this model. Accordingly, there could be a novel relationship between p21 regulation, cell differentiation, and the loss of PC2. Future studies include using *in vivo* injections of EdU to track proliferation and defining cell de-differentiation while comparing other cystic mutants with slower rates of cyst progression.

In conclusion, I hypothesize that p21 is a pre-cystic marker for cystic epithelial cells in polycystic kidney disease. Successful completion of this project could identify p21 as a novel marker for pre-cystic epithelial cells, specify a pathway for cyst inhibition, and outline the cellular response to the loss of PC2 and other ciliary proteins.

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