Characterising a rat model of polycystic kidney disease to identify therapeutic targets

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Introduction. Polycystic kidney disease (PKD) is the most common genetic form of chronic kidney disease and a major risk factor for dementia. PKD and dementia are leading causes of death as there are no disease modifying drugs available. It is not clear how PKD may promote cognitive impairment and dementia, however, systemic inflammation is emerging as a key driver of kidney cyst formation and the development of cognitive impairment. The NLRP3 inflammasome has been implicated in the pathophysiology of other forms of kidney disease but it's contributions in PKD is unknown.

Aims. In a rat model of PKD we aimed to 1) establish the first rat model of PKD-induced cognitive impairment, 2) characterise the inflammatory profile and 3) determine if inhibiting NLRP3 can reduce end-organ damage.

Methods. In the characterisation study, male and female Lewis wild-type (WT) and Lewis polycystic kidney (LPK) rats were studied at 6, 12 and 18 weeks of age. In the intervention study, male and female WT and LPK rats began daily IP injections with the NLRP3 inflammasome inhibitor, MCC950, from 6 weeks of age for 10 weeks.

Results. LPKs had higher BP compared to WT from 6 weeks of age (n=10, $P<0.05$). LPKs had intact recognition memory (n=5-9) but spatial working memory was impaired at 12 and 18 weeks ($P<0.05$). Kidney T cells and macrophages were increased at 6 and 12 weeks but decreased at 18 weeks in LPKs (n=8-10, $P<0.05$). Expression of inflammasomes; NLRP3, NLRC4, AIM2, and components; caspase 1, IL-18 and IL-1b were elevated in LPK kidneys. Inhibition of NLRP3 reduced expression of kidney collagen (n=6-8, $P<0.05$) but overall did not decrease BP, number of kidney cysts or improve kidney function in LPKs.

Discussion. Cognitive impairment was observed in a rat model of PKD from 12 weeks of age which was associated with hypertension and kidney inflammation. Inhibition of NLRP3 inflammasome reduced kidney fibrosis but did not affect blood pressure, cyst growth or kidney function suggesting potential involvement of other inflammasomes in the pathophysiology of PKD.