Kidney and liver cysts in autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) in humans is characterized by a chronic, slowly progressive course in which tissue-displacing, fluid-filled cysts increase in size and number throughout the lifetime of an individual [1]. Molecular genetic studies of human cyst epithelial cells suggest that the disease is caused by a genetic mutation which, with a ‘second hit’, promotes the cystic features; therefore, the disease is recessive on a molecular level [2]. Cysts ultimately lead to necrosis, fibrosis and kidney failure in middle age. As nephrologists, we like images, measurements and mouse models of progressive kidney disease. The liver and cyst growth evaluation done by Doctor and his colleagues, and published in this issue [3], provides me with the opportunity to review mouse models and measurements of cyst progression in experimental and human polycystic kidney disease and polycystic liver disease, as seen in ADPKD, a ‘cholangioliopathy’ [4].

Mouse lines with targeted mutations in Pkd1 or Pkd2, respectively the mouse genes responsible for the equivalent human PKD1 and PKD2 diseases, are powerful tools to study the pathogenesis of the disease and to test new potential therapies. Doctor et al. used here the Pkd2[WS25/−] line [5] bearing a local duplication of the 5′ end of Pkd2 (exon and intron 1). This event resulted in an unstable allele with reversion by intragenic homologous recombination back to a wild-type configuration, or conversion to a true knockout configuration resulting in animals with renal and hepatic disease of various severities that closely mimic human ADPKD. Piontek [6] commented that somatic mutations in that model were random and unregulated, and that there was a possibility for the local duplication to revert to a normal allele by post-mitotic recombination and a time uncertainty about the second hit somatic event. To address these limitations, Piontek et al. developed mice with a floxed allele of Pkd1 (Pkd1cond/cond) [6,7] and were able to induce Pkd1 inactivation at various time points. They showed that inactivation before postnatal Day 13 resulted in severe cystic kidneys within 3 weeks, whereas inactivation at Day 14 and later resulted in cysts only after 5 months. Piontek et al. [7] also demonstrated using nephron segment-specific markers that cysts originated from all tubular segments and were not restricted to collecting duct cells. Natoli et al. [8] used this conditional knockout and two nephronophthisis (jck and pcy) models to demonstrate the beneficial effect of glucosylceramide inhibition. They reasoned that since sphingolipids and glycosphingolipids are major regulators of increased proliferation, apoptosis, and activation of growth regulatory pathways, all mechanisms known to be involved in PKD and nephronophthisis, and since the multiple molecular mechanisms contributing to PKD, including aberrant cilia-cell signalling, intracellular calcium dysregulation, Wnt pathways, cAMP-activated proliferation and the Akt-mediated target of rapamycin (mTOR) pathway could all involve glucosylceramide accumulation, then glycosphingolipid modulation could be a new approach to treat hereditary cystic diseases. Indeed, blockade of kidney glucosylceramide accumulation inhibited cystogenesis in Pkd1 conditional mice as well as in jck and pcy mice. Sphingolipids and glycosphingolipids seem then to be actively involved in cell recognition, proliferation, apoptosis and cell signalling [9]. Images of kidney sections of cystic mice treated with the inhibitor of glycosphingolipid synthesis demonstrated a remarkable decrease in the cysts observed [8]. To sum up, in the mouse models of PKD, there is now an impressive demonstration of less cyst formation and preservation of renal function using non-peptide vasopressin V2 receptor, mTOR inhibitors [1] and kidney glucosylceramide inhibitors.

How can these remarkable advances obtained in experimental models be translated to decrease cyst formation and preserve renal function in human PKD? The most critical challenge to study any drug for human ADPKD is the selection of end points that are clinically relevant, technically achievable and acceptable by regulatory precedent. Quantitative magnetic resonance imaging methods developed in the Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (CRISP) provided accurate estimates of change in renal volume related to renal function: an increase in renal volume of 63.4 mL/year was found [10,11]. A baseline total kidney volume >1500 mL in 51 patients was associated with a decrease in glomerular filtration rate by 4.3 ± 8.07 mL/min/year. As renal growth correlated with a decline in GFR in the subgroup of patients whose total kidney volume was >1500 mL, it was reasoned that effective therapies should slow or stall renal enlargement and, by extrapolation, preserve renal function [12]. However, in the 2-year, placebo-controlled trial of the mTOR inhibitor everolimus, testing >400 patients with a baseline renal volume >1500 mL, no improvement of estimated GFR was observed; yet, there was a slowing of the increase in total kidney volume. In fact, as underlined by Watnick and Germino [12], after a treatment improvement, eGFR declined more rapidly in the everolimus group. In the
same issue of the New England Journal of Medicine, good renal function (GFR > 70 mL/min/1.73 m²) and an average kidney volume of 1 L were observed in sirolimus against placebo in 100 patients with ADPKD. Sirolimus did not slow kidney growth [13]. The Telavaptan Efficacy and Safety in Management of Polycystic Kidney Disease and its Outcome (TEMPO) study involves >1000 patients and prospectively evaluates progression of renal size and kidney function in a placebo-controlled trial with results expected in 2012. Therefore, there is no published demonstration in placebo-controlled trials that any of the pathophysiological pathways identified and tested in mouse studies are amenable to significant improvement or halt progression. It is a formidable task to assess the effects of therapeutic interventions in slowly progressing kidney diseases such as ADPKD where there might be some degree of renal compensation for months masking any subtle decrease in GFR.

The paper by Doctor and colleagues is the second detailed study reporting precise measurements of renal and liver cystogenesis in the same mouse model. Doctor et al. used magnetic resonance imaging, and Stroope et al. [4] used microcomputed tomography scanning. Their results are remarkably similar: at 4 months, kidneys were increased by 40% (Doctor et al., this issue), or cystic volumes represented 40% of kidney parenchyma in 5–7-month-old mice [4]. Hepatic cyst volumes increased from 12% (in 5–8-month-old mice) to 21.6% (9–12-month-old mice). Stroope et al. wrote that, in Pkd2(WS25/-) mice, cystic livers were markedly enlarged occupying the greater part of the abdominal cavity. Of interest, hepatic cysts were lined with single or multiple layers of squamous cholangiocytes, and cystic cholangiocyte cilia were short and malformed, whereas in renal cysts, they appear normal. The rate of cholangiocyte and renal cell proliferation was markedly increased compared to wild type mice [4].

In conclusion, diverse animal models of renal and liver cystogenesis are being progressively deciphered and are providing important tools to understand the pathogenesis of human cystic diseases and to test new compounds intended to stop cyst formation or growth.

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References


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Peritoneal dialysis in the elderly—is its underutilization justified?

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Abstract

Peritoneal dialysis (PD) is underused as a dialysis modality in the elderly population. This is partly due to insufficient information about whether PD confers similar outcomes and quality of life as other modalities. In the BOLDE cross-sectional study, the authors compared dif-