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Murine Models of Polycystic Kidney Disease

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Abstract

Polycystic diseases affect approximately 1/1000 and are important causes of kidney failure. No therapies presently are in clinical practice that can prevent disease progression. Multiple mouse models have been produced for the genetic forms of the disease that most commonly affect humans. In this report, we review recent progress in the field and describe some of the outstanding challenges.

Introduction

In 2003, multiple investigators in the genomics community proposed a project to knockout alleles for all mouse genes. Almost ten years later, the International Knockout Mouse Consortium now boasts of 17,400 mutant murine embryonic stem cells clones and hundreds of conditional mouse strains easily available to investigators all over the world [1]. Furthermore, new advances in gene editing techniques, such as zinc-finger nucleases (ZFNs) and transcription activator–like effector nucleases (TALENs), now hold the promise of inserting virtually any modification in the genome of mice and other vertebrates [2]. At the same time, improvements and cost reduction in high-throughput techniques for phenotypic characterization, from global analysis of gene expression, metabolic profiling to *in vivo* microscopy and whole animal imaging, prelude an era in which the limiting steps are likely to be data analysis and interpretation, rather than model generation. In this short review, we comment on how these developments have shaped our understanding of Polycystic Kidney Disease (PKD).

Text

Using mouse models to understand/treat human disease

Autosomal Dominant Polycystic Kidney Disease (ADPKD)—Arguably one of the nicest success stories of mouse models was the eradication of acute promyelocytic leukemia (APL) by Pandolfi’s group. Over the course of almost 20 years, different gene fusions causing APL were identified and made into mouse models used to test and optimize

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therapies that eventually cured the disease in clinical trials [3]. PKD patients too are now on the verge of benefiting from therapies first tried in mouse models [4].

Mutations in *PKD1* (~85%) or *PKD2* (~15%) cause ADPKD, the most common genetic cause of PKD, affecting 1:1000 individuals [5]. According to a two-hit genetic model, mutations on the previously normal allele of patients heterozygous for *PKD1* or *PKD2* mutations cause the affected cell to clonally expand and form cysts that can arise in any segment of the nephron and usually manifest in adulthood. Consistent with this model, disruption of the mouse orthologs *Pkd1* [6,7] or *Pkd2* [8,9] cause, among other phenotypes, embryonic lethality and bilateral kidney cyst formation starting at E15.5, whereas heterozygotes are viable and normal at birth, but may develop late-onset cysts [9]. By showing that homozygote mice had a range of phenotypes that went beyond ADPKD manifestations and that polycystin-2, the *Pkd2* product, plays a role in right-left symmetry breaking during early embryonic development [7,10–13], these studies suggested that *Pkd1/Pkd2* could play additional, and non-identical, roles at different developmental stages.

Though these were important insights into PKD biology, knockout mice were not an ideal ADPKD model, as the number of kidney cysts in adult heterozygous mice was too low, and embryonic lethality severely limited the use of homozygotes. Other mouse models filled the gap: *Pkd2*^{WS25} has an unstable *Pkd2* allele that undergoes frequent, though random, inactivation [12]; and conditional mice that can be inactivated at different time points/tissues were made [13,14]. Modeling the human disease is still not a trivial matter, however. *Pkd1* inactivation prior to day 14 was shown to result in massive kidney cyst formation within days, whereas inactivation after day 14 results in late-onset kidney disease that takes months to manifest [15]. Though there is some evidence to suggest that the kinetics of cyst formation could depend on the time of inactivation in humans as well [16], this is still an unresolved issue. In addition, despite the ample evidence for a two-hit model, patients homozygous for hypomorphic mutations were a theoretical possibility [5]. Human mutation studies provided supportive evidence [17], but the most compelling data came from a mouse model engineered to be homozygous for the same mutation. These mice survived into adulthood and developed progressive PKD [18]. The existence of these three models: hypomorphic, early- and late-onset poses a quite relevant question: do they share similar pathogenesis and model the same cystogenic process, or do they represent different pathways through which *Pkd1* controls normal tubular diameter? The practical implication of this question is that it is uncertain whether the three models can be interchangeably used when testing therapies.

To date, several orthologous and non-orthologous models have been used to evaluate the therapeutic efficacy of drugs altering pathways allegedly involved in PKD, mostly with positive results (Table 1). In part based on these studies, several drugs were singled out for clinical trials, but these had much more mixed results. Investigators found that mTOR inhibitors were mostly ineffective [19,20] while cAMP lowering drugs had some benefits [4,21]; Table 1). A full discussion of why clinical results may fall short of their pre-clinical counterparts is beyond the scope of this review, but a few general comments are worth making:

- Pharmacodynamics and effective circulating doses generally are not assessed and may differ substantially between rodents and humans. For example, rapamycin was given at up to 5mg/kg in mice [22], compared to 2mg/day in humans [19].
- Most therapies have been tested in early onset models with rapid cyst formation and for short duration. This is very different than the human situation where cysts form slowly over decades and where therapies will likely have to be administered for the rest of the patient's life. This is important not only when considering side effects that may be unacceptable on the long-term but also when considering drugs that may induce up/down-regulation of receptors, with potentially harmful effects in the event of sporadic drug discontinuation. Octreotide administration, for instance, was reported to induce up-regulation of some, but not all, somatostatin receptors [23].
- Outcome evaluation is also not straightforward: if the drugs don't prevent/revert cyst formation, it is unclear that small reductions in the rate of cyst expansion will have any meaningful clinical impact in patient's renal function, quality of life, or life expectancy. It is unclear what a several week to month delay in cyst progression in rodents translates into human outcomes. In the case of everolimus, the drug was highly effective in reducing rate of cyst growth in rodents and somewhat effective in humans, but the drug had no effect on kidney function in the latter [20,24].
- As hinted at above, the selection of a rodent model is not straightforward: *pcy* mice and the Han:SPRD polycystic rat, for instance, have been used as PKD models [25] somewhat interchangeably with orthologous ADPKD models despite the fact that neither results from mutation of either *Pkd1* or *Pkd2*. The *pcy* line has a mutation in *Nphp3*, a nephronophthisis gene, which causes a mostly fibrotic disease in humans, quite distinct from ADPKD and likely to have at least partially different pathogenesis. The Han:SPRD rat has a mutation in *Pkdr1*, a locus not yet associated with clinical disease in humans [26].
- To our knowledge, a systematic study on the effect and magnitude of publication biases in mouse studies is still not available. It is, however, likely not dissimilar to what is reported for meta-analysis of controlled trials: i.e. negative results, because less likely to be published, are not taken into consideration [27].
- Finally, it is worth referring to the important paper by Scott et al. [28]: when confronted with discrepancies between pre-clinical and clinical efficacies of treatments for amyotrophic lateral sclerosis, these authors demonstrated that litter effects, absence of double-blind designs with uniform endpoints, small sample sizes and violations of statistical test assumptions undermined the results. In fact, they demonstrated that random separation of control animals into "experimental" vs. "treatment" groups was likely to yield statistically significant differences when confounding variables were not controlled. This report should be mandatory reading for anyone contemplating preclinical studies using murine models.

Autosomal Recessive Polycystic Kidney Disease (ARPKD)—Despite the challenges and limitations outlined above, it is important to note that ADPKD research has greatly benefited from animal studies. Alas, this is not true for all human cystic kidney diseases. ARPKD is caused by mutations in *PKHD1*, usually presents in infancy and childhood, and is characterized predominantly by dilated/cystic collecting ducts in the kidneys and ductal plate malformation and fibrosis in the liver [29]. Both *PKHD1* and its mouse ortholog extend over large genomic segments and include dozens of exons likely assembled into various transcripts [30–32]. Several mouse models have so far been reported and though all published models to date have liver disease, the kidney phenotype has either been lacking (disruption of exon 40 [33]; disruption of exon 4 [34]), late and/or incompletely penetrant (deletion of exon 2 [35]; deletion of exons 3 and 4 [36]; deletion of exons 1 to 3 [37]; disruption of exons 14 and 15 [38] and/or dependent on mouse strain (Germino, unpublished observation). In addition, homozygosity for a putative null *Pkhd1* allele created by insertion of a stop element in intron 2 only resulted in cystic disease in 3–6 month-old females [39]. It is however possible given the putative complex splicing of the locus that this is not a true null, as only probes to exons 1–18 and 60–67 were tested. In either case, whether complete deletion of *Pkhd1* results in an early ARPKD phenotype or not, it is clear that most deletions fail to consistently recapitulate the human phenotype.

Despite and partly because of their mild phenotypes, ARPKD models can be successfully used to screen for genetic or environmental modifiers likely to play roles in pathogenesis. In fact, we have previously shown that *Pkhd1^{del3-4/del3-4}; Pkd1^{+/-}* mutants have exacerbated ARPKD phenotypes when compared to *Pkhd1^{del3-4/del3-4}* mice, suggesting that *PKHD1* variants could be ARPKD modifiers in humans [36]. Similarly, quantifying the severity of renal and biliary phenotypes in crosses of the *cpk* non-orthologous mouse model, Mrug et al. identified *Kif12* as a potential modifier [40]. Environmental insults are also likely to precipitate cystogenesis. Though this has not yet been shown for *Pkhd1* models, ischemia/reperfusion [41] and toxic injury [42] in late-onset *Pkd1* models seem to accelerate cyst formation.

Using rodent models to identify disease-causing human genes

Rodent models phenocopying PKD, spontaneously found or generated in mutagenesis screens, have helped identify disease-causing human genes. The *Pck* rat was established as a strain with a recessive form of polycystic kidney and liver disease, and the affected gene, mapped by Ward *et al.* to a syntenic region that contained the ARPKD human candidate region, was identified as the likely *Pkhd1* ortholog and used to discover the human *PKHD1* [32]. Though our group independently identified *PKHD1* using positional cloning [31], Ward's work demonstrates the power of mouse genetics.

Two members of the never-in-mitosis A (NIMA)-related kinases (NEKs) - a group thought to coordinate microtubule-dependent processes - have been similarly first identified in spontaneous polycystic kidney mouse models, leading to the detection of disease-causing human homologs [43–46]. *Nek1* was first identified in mice with progressive PKD [43], subsequently shown to phenocopy and be in the candidate region for short-rib polydactyly syndrome (SRPS) type Majewski, finally leading to the recognition of *NEK1* as a SRPS

gene [44]. The *jck* is another recessive polycystic kidney model spontaneously found and later shown to be caused by mutation in *Nek8* [45]. Mutational screening of *NEK8* in patients with nephronophthisis (NPHP) revealed that mutation in this gene is a rare cause of NPHP [46], one that would have been unlikely to be found, had it not been for the mouse model.

Putting it all together: gene networks

Can all these different models with overlapping phenotypes tell us something about how “cystogenes” interact? Indeed they can. The advent of powerful computational methods, associated with a plethora of mouse models, has allowed the identification of several gene networks regulating various aspects of normal kidney development/function and involved in disease processes. Though cystic kidney diseases can be grouped in mostly cystic vs. mostly fibrotic clusters, the characterization of several of the corresponding animal models and subsequent use in drug intervention studies (Table 1) suggest some pathogenic mechanisms are likely conserved (reviewed in [47]). In particular, pathways involved in the establishment of normal tubular diameter are thought to be dysregulated. Reasoning that transcription factors mutated in cystic kidney diseases could be key regulators of epithelial differentiation upstream of cystogenes, Gresh et al. showed that conditional inactivation of *Hnf1 β* in kidney epithelium results in cyst formation and is accompanied by down-regulation of, among others, *Pkd2* and *Pkhd1* [48]. These associations, however, are not necessarily proof of causality, and, as the same group later suggested, other *Pkd2/Pkhd1*-independent pathways could be responsible for the phenotype [49].

Additional support for a *Pkd1/Pkd2/Pkhd1* “cystogenic network” comes from models of autosomal dominant polycystic liver disease (ADPLD). Caused by mutations in *PRKCSH* or *SEC63*, isolated ADPLD is characterized by an ADPKD-like liver phenotype without kidney cysts [50,51]. Using conditional knockout and/or transgenic mice of *Prkcsk*, *Sec63*, *Pkd1*, *Pkd2* and *Pkhd1*, Fedeles et al. showed that ADPLD mouse models have late-onset mild PKD that can be aggravated by heterozygous *Pkd1* or *Pkd2* inactivation, or homozygous *Pkhd1* deletion; furthermore, partial rescue by *Pkd1* overexpression suggests that *Pkd1* dosage is an important factor in cyst formation/growth [52].

These studies offer hypothesis-driven network models for PKD. An alternative way of addressing the same problem is by perturbing genes involved in PKD and applying bioinformatics tools to build gene networks. We have recently concluded a study along these lines, analyzing over 70 kidney samples using *Pkd1* conditional mice [53]. Our data suggest that gene networks in mutant and control samples are not that dissimilar, which would imply that disease status is conferred by differential activation of conserved transcriptional programs. This interpretation has relevant implications: 1) drug therapies globally targeting broad pathways (such as anti-proliferative or broad kinase inhibitors), though potentially capable of halting disease progression, are unlikely to target mutant cells specifically, and may therefore result in prohibitively high levels of unwanted effects; 2) early cysts in ADPKD kidneys are probably not lined with dedifferentiated, immature cells, and it is therefore conceivable that cystic tubes in the early stages of cystic transformation may be made to revert back to normal. We also showed that *Hnf4a* is a disease modifier, which

could have two not mutually exclusive explanations: 1) *Hnf4a* regulates the expression of disease modifier genes; 2) *Hnf4a* is a modifier/marker of altered metabolic status, which is itself the modifier. A recent report suggests metabolic pathways in PKD may in fact be dysregulated and future therapies may be able to exploit these differences [54].

It is a truism to say that everything in biology is information processing. Yet, by looking at PKD from an information-flow perspective, one can reframe the question of understanding and curing PKD as figuring out which information is being lost. In this context, a network approach to PKD provides the framework to understand how subtle differences in gene expression and pathway transduction compound to produce phenotypes, allowing the proposal of combination therapies without a “magic bullet” design, thereby accomplishing normal information processing through alternative pathways. This goal can only be met by intensive perturbations of network systems using various cellular and animal models.

Concluding Comments

Over the last two decades, we went from not knowing which genes caused PKD to being able to systematically dissect different causes, identify abnormal signaling pathways and test therapies. In large measure, mouse models brought about this progress. And though several open questions remain, one can be optimistic that technological advances will keep expanding the horizon of answerable questions.

And yet, there are important caveats that the community should keep in mind. As highlighted in a recent commentary in *Nature* [55], a commitment to model diseases using a handful of species has the advantage of providing a common language to investigators, but at the potential cost of shunning alternative models that could be more useful in specific cases. Put differently: one should identify the questions that really need to be answered and use the models that accomplish that, rather than finding the questions that the usual model can answer. But finally, no matter which model one chooses, extrapolating to human disease is bound to be tricky; after all, people aren't big mice missing tails.

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Table 1

Mouse models used in PKD pre-clinical trials.

Drug	Effect	Model	Clinical Trial
OPC-31260	Lowers cAMP (antagonist of Vasopressin 2 Receptor, VPV2R)	<i>cpk</i> mouse (non-orthologous ARPKD model) [56] Mouse orthologous <i>Pkd2</i> (<i>Pkd2</i> ^{-WS25}) [57]. PCK rat (frameshit in exon 36 of <i>Pkhd1</i> rat ortholog) [58] <i>pcy</i> mouse (missense mutation in the nephronophtisis gene <i>Nph3</i>) [58]	
Tolvaptan (OPC-41061)	Lowers cAMP (antagonist of VPV2R); derived from OPC-31260	PCK rat [59]	TEMPO (1, 445 patients; slower rate of cyst growth in drug group: 5.5% per year versus 2.8% per year; P <0.001 and slower decline in kidney function (reciprocal of the serum creatinine level, -2.61 mg.ml ⁻¹ per year vs. -3.81 mg.ml ⁻¹ per year; P<0.001)) [4]
Octreotide (somatostatin analogue)	Lowers cAMP	PCK rat [60]	42 patients with polycystic liver and kidney disease (liver volume changed 4.95% ± 6.77% in the octreotide group compared to (0.92% ± 8.33%) in the placebo group (P = 0.048, rank-sum test); no difference in kidney function [61]
Pasireotide (somatostatin analogue)	Lowers cAMP	PCK rat and <i>Pkd2</i> ^{-WS25} mouse [23]	
Sirulimus (Rapamycin)/Everolimus	mTOR inhibitor	Han:SPRD rat (non-orthologous ADPKD model) [62–64] <i>Pkd1</i> ^{cond/cond} ; <i>Nestin</i> ^{cre} mouse model (mosaic, random, kidney inactivation) [65] <i>Tg737^{orp/k/orpk}</i> ; <i>TgRsq</i> (non-orthologous polaris mouse model) and <i>bpk</i> (non-orthologous Bicaudal-C mouse model) [22]	433 patients with ADPKD (reduction in the rate of increase in kidney volume: least-square mean differences between everolimus and placebo groups were 54 ml at 1 year (P=0.02) and 71 ml at 2 years (P=0.06); everolimus group had a greater decline in the estimated GFR (by 5.4 ml per minute) than placebo (with a decline of 3.2 ml per minute) (P=0.004) [20]. 100 ADPKD patients in early stages of chronic kidney disease (sirolimus group had no difference in rate of kidney growth [19])