Variable Cyst Development in Autosomal Dominant Polycystic Kidney Disease: The Biologic Context

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ABSTRACT
Patients with autosomal dominant polycystic kidney disease (ADPKD) typically carry a mutation in either the PKD1 or PKD2 gene, which leads to massive cyst formation in both kidneys. However, the large intrafamilial variation in the progression rate of ADPKD suggests involvement of additional factors other than the type of mutation. The identification of these factors will increase our understanding of ADPKD and could ultimately help in the development of a clinically relevant therapy. Our review addresses the mechanisms by which various biologic processes influence cyst formation and cyst growth, thereby explaining an important part of the inter- and intrafamilial variability in ADPKD. Numerous studies from many laboratories provide compelling evidence for the influence on cyst formation by spatiotemporal gene inactivation, the genetic context, the metabolic status, the presence of existing cysts, and whether the kidneys were challenged by renal injury. Collectively, a solid basis is provided for the concept that the probability of cyst formation is determined by functional PKD protein levels and the biologic context. We model these findings in a graphic representation called the cystic probability landscape, providing a robust conceptual understanding of why cells sometimes do or do not form cysts.


Approximately 10% of all patients with ESRD have autosomal dominant polycystic kidney disease (ADPKD). In about 85%–94% of the patients, heterozygous mutations can be found in the polycystic kidney disease 1 (PKD1) gene (approximately 85% of the resolved patients) or the PKD2 gene (15% of the resolved patients).1–4 The kidney is the most severely affected organ, in which thousands of cysts grow from all segments of the nephron, causing massively enlarged kidneys, pain, hematuria, and eventually, renal failure at an age of around 55 years old. Other than the abnormalities in the kidneys, extrarenal manifestations, such as hypertension, cardiovalvular abnormalities, cerebral aneurisms, and cyst formation in liver and pancreas, frequently occur.5 The type of mutation influences the severity of the disease. Generally, PKD1 mutations are more severe than PKD2 mutations, and truncating mutations are more severe than missense mutations.4 However, even between family members who have the same mutation, there can be a large variability, suggesting additional factors that influence disease severity.

THE ROLE OF FUNCTIONAL PKD PROTEIN LEVELS
In the late 1990s, it was found that the remaining functional allele of either PKD1 or PKD2 was frequently mutated or deleted in epithelial cells lining the cyst and that these cells seemed to be of a clonal origin.6,7 These studies supported a two-hit mechanism, in which a heterozygous mutation in one of the PKD genes does not significantly disturb the tubular architecture unless an epithelial cell also loses the second allele. Such cells will ultimately give rise to fluid-filled cysts. Loss of PKD1 or PKD2 expression was, therefore, suggested to be the major trigger for cyst formation. These findings at least partly explained the focal nature of PKD and the relatively large intra– and interfamilial phenotypic variation between patients with ADPKD. The loss of PKD gene expression data was obtained from renal cysts isolated from human end stage ADPKD kidneys. These cysts were, therefore, not analyzed at the time of cyst initiation but probably had been growing for many years before they were isolated. The generation of rodent models for PKD with targeted Pkd1 or Pkd2 mutations or other renal cystic disease–related genes allowed more in–depth studies in the earlier stages of cyst formation.

The first mouse model with a targeted Pkd1 truncation was described in 1997.8 Homozygous knockout mice died prenatally, having several developmental abnormalities and severe PKD. Although heterozygous mice do not have an obvious cystic phenotype, they display

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inappropriate antiureysis, and induced renal injury is exacerbated in heterozygous mice.8–11 Mice with hypomorphic Pkd1 alleles, causing Pkd1 expression to be reduced to roughly 15%–20% of normal Pkd1 expression, had an intermediate phenotype.12–13 These mice survived through embryonic development but developed severe early–onset PKD and had a higher chance of developing fatal dissecting aneurisms.12,14 Also, mice with reduced PKD protein functionality caused by genetic mutations resulting in amino acid substitutions can survive, although the phenotypic severity depends on the mutation.15–17

Tissue-selective inactivation of either the polycystic liver gene Prkcs or Sec63 in mice leads to PKD and polycystic liver disease.18 Prkcs and Sec63 are important in quality control and proper folding of many proteins, including Polycystin-1 (PC1), the protein encoded by Pkd1. The improper folding of PC1 affected trafficking of the mature protein to the primary cilium, an important sensory organelle of which dysfunction often leads to renal cysts. Notably, the severity of the disease greatly depended on the levels of PC1.18 This is further supported by the observation that conditional inactivation of Pkd1 in a Pkd1+/− background usually leads to a more severe phenotype compared with that in a Pkd1+/+ background.19,20 Surprisingly, also, overexpression of Pkd1 has been shown to cause PKD.21,22 These data support that a balanced level of functional PCs is important to maintain tubular architecture.

It is evident that, other than sequence variability in the coding regions of the PKD genes and folding and post-translational regulation of the PCs, transcriptional regulation at the promoter level of the PKD genes is also important. Several pathways, including MEKK1/P53, WNT/β-Catenin, and retinoic acid/Sp1, have been described to regulate the promoter activity of the PKD1 and/or PKD2 genes.23–27 It is likely that variability in the promoter sequence and/or transcriptional regulation of the PKD genes cause expression variability, which could influence susceptibility to cyst formation.

THE ROLE OF THE BIOLOGIC CONTEXT AS A DRIVING FORCE BEHIND CYST FORMATION

It is now well established that, other than the expression levels of PKD genes, the biologic context has substantial effect on cyst formation. Below, we will discuss how the nature of the biologic context either confers susceptibility or resistance to cyst growth.

Timing and Location of PKD Gene Inactivation

Germline inactivation of Pkd1 or Pkd2 by conventional methods leads to severe developmental abnormalities and embryonic lethality, thereby masking important tissue–specific functions during adulthood.8,28 To overcome these issues, several Cre/Lox–P–based systems have been used to inactivate PKD–related genes (e.g., Pkd1, Pkd2, Pkh1d1, Ifi188, etc.) at various stages during life and in various tissues. An extensive overview of those models has been reviewed elsewhere.29 In this review, we will focus largely on the Pkd1 gene, which is the most extensively studied gene. The numerous experimental settings in which this gene has been studied convincingly reveal an important role of the biologic context in PKD progression.

The first studies using conditional and inducible Pkd1 inactivation in rodent models showed that timing of Pkd1 inactivation has enormous effect on the progression rate of PKD.19,30 Pkd1 inactivation before postnatal day (P) 13 led to severe PKD within weeks, whereas Pkd1 inactivation after P13 only resulted in PKD several months later.30 Cre reporter studies showed that the different timing of Cre induction did not lead to different patterns of Cre activity, confirming that the phenotypic differences were caused by the timing of Pkd1 inactivation. Within the same month, an independent study reported similar findings using a similar inducible Cre system, which was controlled by a different promoter.19

Using gene expression profiling, a sharp developmental switch was reported around age P13, which exactly marked the border between the relatively quick PKD progression when Pkd1 was inactivated at P12 and the relatively slow onset when Pkd1 was inactivated at P14.30 In another study, gene expression profiling was performed on mouse kidneys of various ages ranging from embryonic day 19.5 to P35.31 Gene expression changes occurred throughout this time window, but specifically after P14, several processes were downregulated, including DNA replication and cell cycle regulation.31 Although levels of the proliferation marker Ki67 were still high at P14, it is conceivable that certain gene expression programs, including cell cycle regulation, are about to come to an end at P14, which underlies the reduced rate of cyst formation when Pkd1 is inactivated after P14. Notably, disease progression on Pkd1 inactivation at P40 is faster compared with when Pkd1 is inactivated at P90, suggesting that, during adulthood, changes in gene expression programs also continue to be of influence on the PKD progression rate.32

Mice with hypomorphic Pkd1 alleles causing reduced Pkd1 expression develop severe early–onset PKD during the first month of life but then, show a surprising reduction in kidney size during adulthood.13,17,33 Although these findings suggest that, in this model, cyst formation during neonatal development also occurs more rapidly than during adulthood, the reduction in kidney size in adulthood is likely caused by cystic collapse and fibrosis.13,17,33

Newborns with ADPKD sometimes already have relatively large cysts, which can only be explained by a rapid growth of these cysts in utero to reach a diameter at which they can be detected.34 Cysts (ranging from 8 to 81 mm) that were followed by magnetic resonance imaging during adulthood grow at much slower rates.34 Although it is likely that additional germline mutations are underlyong early–onset ADPKD,35–37 these imaging data suggest that, in human patients with ADPKD, the developmental stage of the kidney is also an important parameter affecting cystogenesis. Many smaller cysts below the detection limit of magnetic resonance imaging that
were histologically found in adult ADPKD kidneys suggest that many new cysts continue to form during adult- hood.\textsuperscript{38} The initial growth rate of these newly formed cysts is not known.

The tubular segment in which \textit{Pkd1} is inactivated is another important factor that influences the susceptibility of cyst formation. Crossbreeding \textit{Isp-Pkd1fl/del} mice to LacZ reporter mice\textsuperscript{39} reveals comparable patterns of Cre activation by tamoxifen administration at either P10 or P18 (Figure 1). However, other than the expected progression rate differences, a difference in susceptibility was also observed depending on tubular origin. This was especially prominent when Cre was activated at P10, which led to many rapidly progressing cysts in the outer medulla, the segment with the fewest cells undergoing Cre-mediated recombination by tamoxifen (Figure 1). A study using a similar Cre system driven by a different promotor revealed a more severe PKD phenotype but a rather similar pattern of cyst formation when \textit{Pkd1} was inactivated at P12.\textsuperscript{30} These studies, therefore, suggest that, when \textit{Pkd1} is inactivated around P10, the outer medulla is more susceptible to cyst formation than other regions of the kidney. Notably, in both the P10 and the P18 models, the inner medulla shows many cells in which Cre had been active at the time of tamoxifen administration, but this region seems highly resistant to cyst formation. The causes for these susceptibility differences are not known. We speculate that, especially during neonatal kidney development in the outer medulla, considerable tubule lengthening occurs, which requires the full potential of PKD protein function to coordinate correct directional cell division. Loss of PKD protein function in this context is prone to cyst development.

Collectively, the data suggest that time and tubular–specific genetic programs combined with time and tubular–specific requirement of PC function underlie the spatiotemporal cyst susceptibility differences.

Renal Injury and Cyst Formation

During an episode of renal injury and subsequent repair of the tubule, renal epithelial cells undergo several processes that have some degree of similarity between processes that are at play during renal development, including dedifferentiation, proliferation, and redifferentiation. Therefore, it is conceivable that an episode of renal injury/repair in an adult kidney harboring \textit{PKD1}-deficient cells will accelerate PKD. Several studies tested this hypothesis with various injury protocols, including the administration of the nephrotoxic compound 1,2-dichlorovinyl-cysteine, ischemia-reperfusion, and hypertrophic responses to reduced renal mass after unilateral nephrectomy. Although at various degrees, it was consistently found that PKD progressed faster if adult inactivation of \textit{PKD1}-related genes was followed by some form of renal injury.\textsuperscript{20,32,40–42} Notably, macrophages preferentially accumulated near the initial cystic regions as well (Figure 1B). It has been shown before that \textit{Pkd1}-deficient cells in cystic regions attract macrophages, which further enhances cyst formation.\textsuperscript{46} The exact nature of macrophages within a complex tissue environment is difficult to predict by the analysis of a limited number of markers.\textsuperscript{47} However, the observations that depletion of macrophages by liposomal Clodronate treatment inhibited proliferation and cyst growth and that macrophages in kidneys from patients with ADPKD and patients with ARPKD express markers, including CD163, suggest that the macrophages in a cystic environment preferentially switch to an M2 or heal mode and stimulate cyst growth.\textsuperscript{46–48}

Modifying Genes and Modifying Diets

Many signaling pathways are involved in driving the continuous changes within the cystic kidney. It is likely that the genetic background will influence the activity of those pathways and could, therefore, modulate disease severity. The search for modifier genes is complicated and requires large cohorts to find alleles of significance. A genotype-phenotype correlation study analyzing 173 candidate genes identified three different single–nucleotide polymorphisms in the \textit{DKK3} gene, which correlated with renal function in two cohorts of patients with ADPKD. \textit{DKK3} is functionally related to the WNT signaling pathway, which has been associated with cyst formation before, and could, therefore, possibly underlie some of the phenotypic variation between patients.\textsuperscript{49} Other potential modifiers suggested from specific pedigrees are the CFTR-chloride transporter and genes involved in hypertension as well as additional mutations in the cystic genes themselves.\textsuperscript{35–37,50–53}

Another convincing observation that supports the role of the genetic context is the difference in renal cystic disease progression between men and women with ADPKD. Also, in mice, the difference has been noticed.\textsuperscript{19,54} Gene expression profiling revealed that the
The mechanism of cyst formation is not different between male and female mice but that the degree of altered signaling and metabolism is underlying the differences in progression rate. This was confirmed by the observation that a lower dietary lipid content was associated with a slower progression of PKD in mutant mice. Also, caloric restriction by reduced food intake or targeting glucose metabolism by 2-deoxyglucose treatment slows PKD progression in several animal models. Although the involvement of pathways, including mammalian target of rapamycin and LKB1/AMPK, varied between the different experimental settings, the data consistently point to a role of altered metabolism in ADPKD, which can be modulated by changing the diet. Recently, a small 4-week clinical trial has been completed, in which patients with ADPKD followed a strict diet aimed to study feasibility of reducing the intake of sodium, protein, and acid precursors and increase water intake. Increasing water intake aims to reduce plasma levels of arginine

![Figure 1](image-url). Timing and location of Pkd1 inactivation, cysts, and macrophages influencing the PKD phenotype. (A) The pattern of Cre activity was determined by crossbreeding the tamoxifen (Tam)–inducible iKsp–Pkd1<sup>fl/fl</sup> mice with an LacZ reporter strain (lower panel). A similar pattern of Cre activity was revealed by LacZ staining of kidneys from mice that received Tam at either P10–P12 (P10) or P18–P20 (P18). However, despite this similar pattern of Cre activity, Tam administration at these different ages dramatically affected the progression rate of cyst formation: hematoxylin and eosin–stained kidney sections are shown (upper panel) from an iKsp–Pkd1<sup>fl/fl</sup> mouse euthanized 3 weeks after Tam administration at P10–P12 (P10) and an iKsp–Pkd1<sup>fl/fl</sup> mouse euthanized 10 weeks after Tam at P18–P20 (P18). Also, the tubular origin in which Pkd1 is inactivated seems to influence susceptibility. This is especially prominent in the P10 model, in which the outer medulla (OM) is the most severely affected region; however, this region has the fewest Pkd1–deficient cells. (B) iKsp–Pkd1<sup>fl/fl</sup> mice had been treated with low-dose Tam at P40 (leading to Pkd1 inactivation in about 8% of cells) and were euthanized at an age of 9 months. Kidneys were harvested and stained with anti-F4/80 (brown), which in mouse studies, is frequently used as a general marker for macrophages. Whole-kidney sections stained with anti-F4/80 are shown from an iKsp–Pkd1<sup>fl/fl</sup> mouse at a relatively mild stage of PKD (upper left panel) and an iKsp–Pkd1<sup>fl/fl</sup> mouse at a somewhat more advanced stage of PKD (lower left panel). Both mice show clusters of cysts but still had normal kidney function on the basis of measurements of the urea concentration in blood. Enlargements of F4/80 images are shown in right panel. The wild–type (WT) kidney image was taken from an anti–F4/80–stained kidney section from an age–matched WT control mouse. Images 1–3 are enlargements of the areas indicated in the whole sections. In regions not affected by cyst formation (image 2), F4/80 staining is comparable with that in the WT kidney. Regions with cysts (images 1 and 3) show increased F4/80 staining in the interstitial compartment around normal and slightly dilated tubules. C, cortex; IM, inner medulla.
vasopressin, which is an antidiuretic hormone, a driver of intracellular cAMP levels in the collecting duct, and known to be highly involved in PKD progression. In fact, the drug tolvaptan, which modestly slowed PKD progression in a large 3-year phase 3 clinical trial,\(^6\) is an antagonist for the same receptor. Patients with ADPKD seemed highly motivated to comply with these dietary changes, which paves the way for dietary intervention strategies.\(^5\)

Figure 2. The cystic probability landscape of renal epithelial cells. (A) Each situation requires a certain level of expression of functional PKD proteins to ensure normal homeostasis (left panel). When the expression deviates from the normal situation, the expression is either too low or too high (x axis). The extent to which certain biologic processes influence the probability of cyst formation is depicted on the z axis. Sometimes the effect is very low, such as the biologic context of an adult kidney, and sometimes the effect can be very high, such as the biologic context of a developing kidney. The combination of the PKD protein expression levels (x axis) and the particular biologic context (z axis) will determine a certain probability of cyst formation, which is indicated on the y axis. The combination of all theoretical possible situations results in the cystic probability landscape. The circles indicate examples of locations of renal epithelial cells within the landscape (the circle size correlates to how frequently such situations might occur; right panel). Throughout life, renal epithelial cells from healthy individuals will undergo certain biologic processes (examples are indicated in boxes). However, because PKD protein expression levels (for these examples, PKD1 expression is indicated for simplicity) are properly regulated in these cells, the probability that these cells will form cysts is low. (B) Throughout life, renal epithelial cells from patients with ADPKD move differently within the landscape. During renal development (Developm.), most cells have a heterozygous PKD1 mutation (PKD1\(^{+/-}\)), but generally, these cells do not form cysts unless some cells also lose the second allele (PKD1\(^{-/-}\); left panel). Also, cells that have two hypomorphic alleles of PKD1 (PKD1 hypo.) have a high risk of developing cysts. Although the probability of cyst formation increases when a cell loses PKD1 during adulthood or has two PKD1 hypo., cyst formation is rare under physiologic conditions (center panel). However, during an episode of local renal injury, PKD1\(^{-/-}\) cells have a much higher probability to form cysts. Also, overexpression of PKD1 (PKD1\(^{+++}\)) leads to increased probability of cyst formation. As PKD progresses, the number and size of cysts increase, leading to injury-like responses caused by the existing cysts themselves, infiltrating cells, etc. (right panel). This leads to changes in the biologic context of resident PKD1-deficient cells and generally, situations with increased risk of cyst formation. Ultimately, these various biologic processes will push renal epithelial cells with aberrant PKD1 expression toward the higher regions of the probability landscape, causing additional increase in the numbers of cysts.
THE CYSTIC PROBABILITY LANDSCAPE AS A CONCEPTUAL VIEW ON CYST FORMATION

The data from various laboratories using several distinct models for PKD as reviewed above provide a solid basis for the concept that the probability that a renal epithelial cell will form a cyst is a function of its PKD protein levels and its particular biologic context. For example, if a renal epithelial cell has markedly reduced levels of PKD1 expression during renal development, it is much more likely to form a cyst within a certain amount of time than if the same cell would be situated in an adult kidney. Other situations that affect the probability of cyst formation are the segmental origin of renal epithelial cells, the balance between the requirement and the availability of functional PKD protein expression, and whether the cell is situated in a region near other cysts or within a region affected by injury. These and all other theoretical situations can be presented in an hypothetical graph, which we call the cystic probability landscape (Figure 2A).

The shape of this landscape is an estimation on the basis of the current knowledge about the parameters influencing cystogenesis.

The location of a renal epithelial cell within this landscape is, therefore, determined by the expression levels of functional PKD proteins and the biologic context, which together determine a certain probability that this cell will form a cyst (for simplicity, the relative PKD1 expression is indicated, but the same could be relevant for other PKD-related genes, although these genes are not as extensively studied as the PKD1 gene).

Example locations corresponding to a certain risk level of cyst formation on the basis of known situations are shown in Figure 2. Biologic processes that occur in the developing kidney, the adult kidney, near renal injury, or near cysts do not significantly affect the probability of cyst formation for renal epithelial cells with functional PKD genes (Figure 2A), but the same processes dramatically affect the probability of cyst formation for cells with aberrant PKD1 expression (Figure 2B). The cystic probability landscape, therefore, provides conceptual answers to the questions of why certain cells under particular conditions will form cysts and why other cells do not form cysts. However, although many studies support the shape of the landscape in the region with low expression of PKD1, the overexpression side is more speculative because of the limited number of overexpression studies.

CONCLUDING REMARKS

Multiple model systems and human ADPKD data provide compelling evidence to support that PKD progression is influenced by the biologic context in which functional PKD protein expression is compromised.17,19,20,30,32–34,40–45,54–58 It is unlikely that the observed variability in the PKD phenotype is merely caused by the different model systems used in these studies, because even within one single tamoxifen-inducible, kidney–specific Pkd1 deletion mouse model (iKsp-Pkd1del), nine experimental settings performed in our laboratory

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Table 1. Different PKD1 inactivation and injury strategies with iKsp-Pkd1del mice lead to different phenotypes

<table>
<thead>
<tr>
<th>Tam/Injury Protocol</th>
<th>Origin of Cysts</th>
<th>Short Description of Renal Cystic Phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tam at P4 (200 mg/kg to lactating mother; pups receive Tam through mother’s milk)</td>
<td>DT &gt; CD &gt; PT</td>
<td>Rapid formation of numerous large cysts within 1 mo</td>
<td>19</td>
</tr>
<tr>
<td>Tam at P10 (6 mg/kg oral)</td>
<td>DT &gt; CD &gt; PT</td>
<td>Rapid formation of numerous large cysts within 1 mo</td>
<td>66</td>
</tr>
<tr>
<td>Tam at P18 (150 mg/kg oral)</td>
<td>DT = CD = PT</td>
<td>Synchronized formation of many cysts; renal failure around 10–12 wk after Tam</td>
<td>66</td>
</tr>
<tr>
<td>Low-dose Tam at P40 (10 mg/kg oral)</td>
<td>PT &gt; DT &gt; CD</td>
<td>Very few cysts within the first 6 mo after Tam; first cysts induce clustered formation of new cysts; severe PKD around 10 mo after Tam</td>
<td>20</td>
</tr>
<tr>
<td>Low-dose Tam at P40 (10 mg/kg oral) + DCVC- (15 mg/kg intraperitoneal) and/or unilateral nephrectomy–induced injury</td>
<td>PT &gt; DT &gt; CD</td>
<td>Similar PKD phenotype compared with mice only treated with low-dose Tam at P40 but slightly faster</td>
<td>20</td>
</tr>
<tr>
<td>Tam at P40 (200 mg/kg oral)</td>
<td>PT &gt; DT &gt; CD</td>
<td>Synchronized formation of many cysts, renal failure around 14–16 wk after Tam</td>
<td>20,64,69,75</td>
</tr>
<tr>
<td>Tam at P40 (200 mg/kg oral) + unilateral nephrectomy–induced injury</td>
<td>PT &gt; DT &gt; CD</td>
<td>Similar PKD phenotype compared with mice only treated with Tam at P40 but about 30% faster</td>
<td>20</td>
</tr>
<tr>
<td>Tam at P90 (200 mg/kg oral)</td>
<td>PT &gt; DT &gt; CD</td>
<td>Synchronized formation of many cysts; renal failure around 22 wk after Tam</td>
<td>19,32</td>
</tr>
<tr>
<td>Tam at P90 (200 mg/kg oral) + DCVC-induced injury (15 mg/kg intraperitoneal)</td>
<td>PT &gt; DT &gt; CD</td>
<td>Similar PKD phenotype compared with mice only treated with Tam at P40 but about 40% faster</td>
<td>32</td>
</tr>
</tbody>
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At various P days, tamoxifen (Tam) treatments (always on 3 consecutive days starting from the indicated ages using the indicated dosages) were performed to inactivate Pkd1 in iKsp-Pkd1del mice (all on C57BL/6 background). In some strategies, renal injury by injection of the nephrotoxic compound 1,2-dichlorovinylcysteine (DCVC) or unilateral nephrectomy was performed, and/or a lower dose of Tam (low-dose Tam) was administered to reduce the number of Pkd1-deficient cells. These protocols are indicated in column 1. In column 2, the relative abundance of cysts is shown in proximal tubules (PT), distal tubules (DT), and collecting ducts (CD). Also, a short description of the cystic phenotypes and the references are given. Notably, although the Pkd1 mutation and genetic background are always the same, the renal cystic phenotype varied considerably depending on the experimental procedure performed. Detailed descriptions of various other rodent models for PKD has been reviewed elsewhere by Happé et al.29

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led to distinct cystic phenotypes, despite the fact that the mutation and the genetic background (C57BL/6) were always the same (Table 1). This led us to propose the cystic probability landscape, which integrates these findings in a visual representation. The conditions in kidneys between patients with ADPKD probably vary considerably depending on individual combinations of modifying genes, lifestyle, nephron number, local renal injury insults, and so on. The cystic probability landscape, therefore, suggests that the risk of cyst development by renal epithelial cells varies between patients depending on their specific conditions and provides a conceptual understanding for the inter- and intrafamilial variation that is observed between patients with ADPKD. However, how the different situations affect the underlying signaling pathways that ultimately determine the probability that cells will form cysts is extremely complex and is not yet fully understood. Many suggestions for contributing signaling pathways have been reviewed elsewhere. Some of those, including cAMP, Src/Ras/Raf/MEK/ERK, JAK/STAT, Activin signaling, AMPK, glucose metabolism, calcium signaling, mamalian target of rapamycin, and SIRT1, hold promising potential as therapeutic targets.

Although a thorough prioritization of these and other pathways is challenging and yet to be made, reduction of intracellular cAMP levels has already shown clinical benefit by tolvaptan treatment, and a similar strategy is currently assessed in clinical trials using somatostatin analogs. Given the complex signaling within the ADPKD kidney, we speculate that combination treatments and/or modulation of pathways by dietary strategies could contribute to finding an optimal balance between side effects and efficacy.

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DISCLOSURES

None.

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