POLYCYSTIC KIDNEY DISEASES ARE A LEADING CAUSE OF END-STAGE RENAL FAILURE AND A COMMON INDICATION FOR DIALYSIS OR RENAL TRANSPLANTATION. RECENT ADVANCES HAVE LED TO INSIGHTS INTO MECHANISMS UNDERLYING THE CAUSE AND PROGNOSIS OF THESE DISEASES AND SUGGEST NEW DIRECTIONS FOR TREATMENT.

Polycystic kidney disease may arise sporadically as a developmental abnormality or may be acquired in adult life, but most forms are hereditary. Among the acquired forms, simple cysts can develop in kidneys as a consequence of aging; dialysis, drugs, and hormones can cause multicystic disease and renal cysts are often secondary manifestations of genetic proliferative syndromes. The inherited polycystic kidney diseases, which are due to germ-line mutations in single genes, inherited as mendelian traits, include autosomal dominant and autosomal recessive polycystic kidney disease, nephronophthisis, and medullary cystic diseases. The age at onset, the severity of symptoms, and the rates of progression to end-stage renal failure or death vary widely in this group of diseases.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease, the most common form of polycystic kidney disease, occurs in 1 in 800 live births. It affects 500,000 persons in the United States and 4 million to 6 million worldwide and is the reason for hemodialysis in 7 to 10 percent of patients. There are two types: type I is caused by mutations in the PKD1 gene and accounts for 85 to 90 percent of cases, and type II is caused by mutations in the PKD2 gene and accounts for 10 to 15 percent of cases (Table 1). The protein products of these two genes, polycystin-1 (Fig. 1A) and polycystin-2 (Fig. 1B), occur on renal tubular epithelia. Polycystin-1 is a membrane receptor capable of binding and interacting with many proteins, carbohydrates, and lipids and eliciting intracellular responses through phosphorylation pathways, whereas polycystin-2 is thought to act as a calcium-permeable channel. The two types of autosomal dominant polycystic kidney disease have similar pathological and physiological features, but type II disease has a later onset of symptoms and a slower rate of progression to renal failure; thus, patients have a longer life expectancy (69.1 years) than those with type I disease (53.0 years). Some patients with typical features of autosomal dominant polycystic kidney disease have no mutations in PKD1 or PKD2, suggesting that there may be a rare third form of the disease, although the proposed gene — PKD3 — has not been identified. Patients with mutations in both the PKD1 and PKD2 genes (transheterozygotes) have a more severe clinical course than those with mutations in only one of the genes.

Tremendous cystic enlargement of both kidneys is characteristic of autosomal dominant polycystic kidney disease. Patients often present with hypertension, hematuria, polyuria, and flank pain and are prone to recurrent urinary tract infections and renal stones. In addition to the presence of hundreds to thousands of renal cysts, up to 10 to
20 cm in diameter, clinically significant cysts are also common in the liver (especially in women), pancreas, and intestine. Patients have an increased risk of aortic aneurysms and heart-valve defects, and some kindreds have five times the risk in the general population of sudden death from ruptured intracerebral aneurysms.\textsuperscript{10} AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Autosomal recessive polycystic kidney disease is much rarer than the autosomal dominant form, with an incidence of 1 in 20,000 live births, and often causes fetal or neonatal death owing to tremendous

Table 1. Characteristics of Inherited Polycystic Kidney Diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism of Inheritance\textsuperscript{*}</th>
<th>Aberrant Gene</th>
<th>Chromosomal Location</th>
<th>Length of Transcript</th>
<th>Protein Encoded</th>
<th>Molecular Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycystic kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>AD</td>
<td>PKD1</td>
<td>16p13.3</td>
<td>14.5</td>
<td>Polycystin-1</td>
<td>462</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td>PKD2</td>
<td>4q21</td>
<td>5.6</td>
<td>Polycystin-2</td>
<td>110</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>AR</td>
<td>PKHD1</td>
<td>6p21–23</td>
<td>16.2</td>
<td>Fibrocystin</td>
<td>447</td>
</tr>
<tr>
<td>Nephronophthisis</td>
<td>Juvenile</td>
<td>AR NPH1</td>
<td>2q12–13</td>
<td></td>
<td>Nephrocystin</td>
<td>83</td>
</tr>
<tr>
<td>Infantile\textsuperscript{†}</td>
<td>AR</td>
<td>NPH2</td>
<td>9q22–31</td>
<td>5</td>
<td>Inversin</td>
<td>98</td>
</tr>
<tr>
<td>Adolescent</td>
<td>AR</td>
<td>NPH3</td>
<td>3q21–22</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Medullary cystic kidney disease</td>
<td>AD</td>
<td>MCKD1</td>
<td>1q21</td>
<td>?</td>
<td>?</td>
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<tr>
<td></td>
<td>AD</td>
<td>MCKD2</td>
<td>16p12</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

\textsuperscript{*} AD denotes autosomal dominant, and AR autosomal recessive. \textsuperscript{†} Data are from Otto et al.\textsuperscript{5}
A Polycystin-1

B Polycystin-2

C Nephrocystin

D Fibrocystin

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bilateral enlargement of the kidneys, impaired lung formation, and pulmonary hypoplasia. Renal failure and hepatic fibrosis develop in most babies who survive the perinatal period. The disease is characterized by the expansion and elongation of collecting tubules into multiple small cysts and by biliary dysgenesis. Mutations in the PKHD1 gene cause autosomal recessive polycystic kidney disease11,12 (Table 1 and Fig. 1D). The identification of a mild form of the disease13 suggests that additional genes are involved.

**Familial Nephronophthisis**

Familial nephronophthisis is inherited as a recessive trait. Three distinct types — juvenile, adolescent, and infantile — are caused by mutations in the NPH1 (Fig. 1C), NPH2, and NPH3 genes, respectively.14-16 In nephronophthisis, both kidneys are shrunken and the renal cysts are restricted to the medulla at its border with the cortex. The typical clinical manifestations are salt wasting, growth retardation, anemia, polyuria, and progressive renal insufficiency.

**Medullary Cystic Kidney Disease**

The two distinct types of medullary cystic kidney disease are caused by mutations in either the MCKD1 or MCKD2 gene.17,18 These diseases are also characterized by bilaterally shrunken kidneys, cysts restricted to the renal medulla, salt wasting, and polyuria. But unlike nephronophthisis, medullary cystic kidney diseases are inherited as autosomal dominant traits (Table 1), and clinically milder, and typically first appear in adulthood.

**Cell Biology**

In autosomal dominant polycystic kidney disease, the thousands of large, spherical cysts of various sizes throughout the cortex and medulla are derived from every segment of the nephron. The tubule wall, which is lined by a single layer of epithelial cells, expands and then rapidly closes off from the tubule of origin (Fig. 2B).1 By contrast, in autosomal recessive polycystic kidney disease, the smaller, elongated cysts arise as ectatic expansions of collecting ducts and maintain contact with their nephron of origin (Fig. 2C). In nephronophthisis and medullary cystic kidney disease, the cysts are restricted to the corticomedullary border and may be derived from collecting ducts and distal tubules. Despite these differences among polycystic kidney diseases, common features control the formation and enlargement of renal cysts.19

**Proliferation and Apoptosis**

A precisely controlled balance between cellular proliferation and programmed cell death (apoptosis) is essential for normal growth and differentiation of the kidney and maintenance of normal renal structure after birth. These fundamental processes are disturbed in polycystic kidneys. In both autosomal dominant and autosomal recessive polycystic kidney disease, apoptosis is abnormally persistent20 and can destroy much of the normal renal parenchyma, thereby allowing cystic epithelia to proliferate. The importance of apoptosis has been highlighted in knockout mice, in which the inactivation of inhibitors of apoptosis (bcl-2 or activating protein 2β [AP-2β]) causes cystic kidney disease.21,22 Rodent models of polycystic kidney disease are listed in Supplementary Appendix 1 (available with the full text of this article at www.nejm.org).

The proliferation of renal tubular epithelial cells ceases before birth, but cystic epithelia proliferate abnormally throughout life in patients with autosomal dominant polycystic kidney disease.23 Moreover, cultured epithelial cells from these patients have an increased intrinsic capacity for proliferation and survival. Several genetic manipulations that cause the proliferation of tubular epithelial cells in mice also lead to renal cystic disease24-27 (see Supplementary Appendix 1).

Epidermal growth factor (EGF) has an important role in the expansion of renal cysts. Epithelial cells from cysts from patients with the autosomal dominant form and from those with the autosomal recessive form are unusually susceptible to the proliferative stimulus of EGF. Moreover, cyst fluids from the former group of patients contain mitogenic concentrations of EGF, and this EGF is secreted into the lumens of cysts in amounts that can induce cellular proliferation.28 The overexpression and abnormal location of EGF receptors on the apical (luminal) surface of cyst-lining epithelia creates a sustained cycle of autocrine–paracrine stimulation of proliferation in the cysts28 (Fig. 3).

Genetic experiments in mice have also shown the importance of the overexpression of EGF receptors in the formation of renal cysts.29 and this work has led to the development of specific inhibitors of the EGF-receptor tyrosine kinase, which have re-
duced the number of cysts and extended the life span of mice with polycystic kidney disease. This class of small-molecule inhibitors of tyrosine kinase is now under investigation in phase 1 and 2 clinical trials in adults with polycystic kidney disease to determine whether they slow the expansion of cysts and the decline in renal function.

EGF receptors are also expressed in the apical membranes of collecting-tubule epithelia in normal fetal kidneys (Fig. 3). Whereas basal EGF receptors in normal adult epithelia are comprised of homodimers, the apical EGF receptors consist of heterodimers of EGF receptor and erb-b2. The importance of this EGF-receptor variant, erb-b2, is illuminated by the fact that renal cysts form in transgenic mice that overexpress erb-b2 and that erb-b2 inhibitors have a protective effect in vitro on cells from patients with autosomal dominant polycystic kidney disease. These observations suggest that erb-b2 inhibitors might have therapeutic value.

Additional growth factors, cytokines, and lipid factors, as well as adenosine triphosphate (ATP) and cyclic adenosine monophosphate (cAMP) in cyst fluids, have proliferative effects on epithelial cells in vitro. These factors may stimulate EGF-dependent growth of cysts.

SECRETION
The net reabsorption of fluid in the normal kidney is brought about by sodium ion gradients established by the sodium pump (Na+/K+-ATPase) in the basolateral tubular cell membrane and by multiple ion and fluid transporters and channels in apical and basolateral sites. In kidneys of patients with polycystic kidney disease, Na+/K+-ATPase is abnormally located in the apical (luminal) cell membranes of tubular epithelia (Fig. 3) and the Na+,K+-2Cl− symporter is misplaced to the basal surface of the epithelia.

Molecular studies of the α and β subunits of the Na+/K+-ATPase complex have shown that normal adult kidneys contain α1β1 complexes, which

Figure 2. Mechanisms of Cyst Formation in Polycystic Kidney Disease.
Cysts originate as expansions of the renal tubule (Panel A). In autosomal dominant polycystic kidney disease, cystic outpushings arise in every tubule segment and rapidly close off from the nephron of origin (Panel B). By contrast, in autosomal recessive polycystic kidney disease, cysts are derived from collecting tubules, which remain connected to the nephron of origin (Panel C).
are located in the basolateral region of the tubule, whereas the kidneys of patients with polycystic kidney disease contain α1β2 complexes in the apical membrane.\(^{39}\) In the normal fetus, Na\(^+\)/K\(^+\)–ATPase is also composed of α1β2 complexes and occurs on the apical membranes of renal tubules.\(^{40}\) It seems that in autosomal dominant polycystic kidney disease, a failure to down-regulate the transcription of the β2 isoform after birth facilitates the erroneous placement of Na\(^+\)/K\(^+\)–ATPase in the apical membrane.

Additional transport-related features of cysts include the presence of aquaporin 1 or aquaporin 2 water channels in cyst epithelia from patients with autosomal dominant polycystic kidney disease and of aquaporin 2 alone in cysts from patients with the autosomal recessive form.\(^ {41}\) The high levels of ATP released by apical membranes in patients with the autosomal dominant form may further exacerbate secretion.\(^ {42}\) Intracellular cAMP levels are also important regulators of secretion in cysts and regulate the cystic fibrosis transmembrane conductance regulator chloride channels in the apical membranes of cystic epithelia from patients with autosomal dominant polycystic kidney disease.\(^ {43}\)

**Cell–Matrix Interactions**

Abnormalities in the basement-membrane structure, interstitial matrix composition, the levels of matrix metalloproteases and their inhibitors, and the expression of integrin receptors occur in patients with polycystic kidney disease.\(^ {40}\) Thickened basement membranes, alterations in matrix composition, and abnormal numbers of integrin receptors are frequent in autosomal dominant as well as autosomal recessive polycystic kidney disease and juvenile nephronophthisis. These alterations cause marked functional disturbances. For example, epithelia from patients with autosomal dominant polycystic kidney disease are more adherent to matrices.\(^ {40}\)

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Figure 3. Polarization of Epidermal Growth Factor Receptor (EGFR) and Na\(^+\)/K\(^+\)–ATPase in Epithelium from a Normal Fetus, a Normal Adult, and a Patient with Polycystic Kidney Disease.

Fetal and epithelial cells and epithelia from patients with polycystic kidney disease express heterodimeric complexes of EGFR and erb-b2 as well as heterodimeric complexes of α1β2 Na\(^+\)/K\(^+\)–ATPase at apical-cell membranes. In normal adults tubular epithelia express homodimeric complexes of epidermal growth factor receptor and homodimeric complexes of α1β1 Na\(^+\)/K\(^+\)–ATPase at basolateral membranes.
made up of collagen type I or IV than are normal epithelia and have decreased migratory capacities against growth factor gradients. Such defects may impair the cell movements required for morphogenesis of the kidney.

Genetic experiments in mice have shown that inactivation of several matrix adhesion receptors and focal adhesion complex–associated proteins causes the formation of cysts. Similarly, overexpression of polycystin-1 or β-catenin (Wnt) causes cysts. The migratory defect of epithelial cells from patients with autosomal dominant polycystic kidney disease can be reversed by inhibitors of the Wnt pathway. These molecules may have potential therapeutic applications.

**POLARITY**

The normal adult nephron is a segmented structure lined by at least 15 distinct types of highly polarized epithelia. The polarized distribution of enzymes, ion transporters, channels, pores, growth factor, and matrix receptors facilitates normal vectorial function (directional transport) and the control of cell division, differentiation, and maturation. In autosomal dominant and autosomal recessive polycystic kidney disease, alterations in the polarity of membrane proteins include aberrant location of Na+/K+-ATPase, EGF receptors, cathepsin B, matrix metalloproteinase 2, and E-cadherin in the apical-cell membrane rather than the basolateral membrane. Polarization of proteins occurs during the maturation of nephrons in utero and proceeds by means of the regulated switching of gene expression. Persistent expression of fetal forms of Na+/K+-ATPase and EGF receptors suggest the presence of a block in the maturation program.

The protein encoded by PKD1, polycystin-1, has defects in polarity and trafficking in patients with autosomal dominant polycystic kidney disease. In normal renal epithelia, polycystin-1 is confined to lateral cell membranes at sites of cell–cell adhesion (adherens junctions) and cell–matrix contacts (focal adhesions), whereas in cystic epithelia, most of this protein is intracellular.

**SIGNAL TRANSDUCTION**

Many intracellular signal-transduction pathways have been implicated in the etiologic process of polycystic kidney disease. The PKD1, PKD2, and NPH1 gene products can themselves activate intracellular signaling cascades that regulate cell proliferation, migration, and differentiation. Integration of these pathways is essential for the cell movements underlying morphogenesis and the cell maintenance of renal tubules with correct luminal diameters. Polycystins initiate these pathways through interactions with several proteins at the cell–cell adherens junctions and cell–matrix focal adhesion complexes. Loss of the focal adhesion function in mutant polycystin-1 results in the failure to recruit the focal adhesion kinase in patients with autosomal dominant polycystic kidney disease (Fig. 5), and mutation of nephrocytin in nephronophthisis causes the formation of cysts. Additional regulation of the function of polycystins occurs by means of G proteins, phospholipase C, and tyrosine kinases. Dephosphorylation by receptor protein tyrosine phosphatases, and the intracellular second messengers calcium and cAMP. Current evidence suggests that complex patterns of signaling from polycystins, intracellular second messengers, and growth factors coordinate the regulation of the proliferation, differentiation, and morphogenesis of renal tubular cells through interactions with protein complexes linked to the actin cytoskeleton, intracellular signaling cascades, and the regulation of gene transcription (Fig. 4). Perturbations of these regulatory mechanisms by mutations in PKD1, PKD2, or NPH1 disrupt these processes (Fig. 4).

**CILIA**

The principal cells of the renal collecting tubule have a solitary central cilium, the function of which is obscure. Intriguingly, two mutant mouse strains with autosomal recessive polycystic kidney disease (Tg737 and cpk) have abnormal ciliary structure or function, and their encoded proteins (polaris and cystin) colocalize with polycystins in collecting-tubule cilia. However, it is not known whether these abnormalities apply to autosomal recessive polycystic kidney disease in humans, which involves a mutant PKHD1 gene. Genetic studies in a worm (Caenorhabditis elegans) and functional studies in cell culture and a Pkd-1 mutant mouse suggest a sensory role for the cilium in autosomal dominant polycystic kidney disease.

**MOLECULAR BIOLOGY**

**PKD GENES AND MUTATIONS**

A wide range of mutations in PKD1 or PKD2 can cause autosomal dominant polycystic kidney dis-
ease. These mutations are spread across the entire sequence of these genes and include deletions, insertions, and frame shifts and splicing, nonsense, missense, and point mutations. In kindreds, most mutations encode a truncated protein and are unique to a single family. PKD1, a large gene with 46 exons, encodes a 14.5-kb transcript (Table 1). The existence of additional PKD1-like homologous genes upstream of the 5′ region of PKD1 complicates mutation analysis considerably. More than 100 mutations of PKD1 have been identified. By contrast, PKD2, a simpler 15-exon gene, encodes a smaller 5.6-kb transcript (Table 1). More than 75 mutations of PKD2 have been identified, again mainly of the inactivating type.

Patients with autosomal dominant polycystic
Kidney disease are heterozygotes, having inherited one mutant and one normal (wild-type) allele of PKD1. A “two-hit” mechanism has been proposed to explain how cysts develop. This mechanism requires not only a germ-line mutation of PKD1 or PKD2 but also an additional somatic mutation in the wild-type gene to initiate the formation of cysts. Although such second hits (point mutations) do indeed occur within individual cysts, the frequencies are low (17 percent in PKD1 and up to 43 percent in PKD2), and polycystin protein is seen in most cyst epithelial cells of kidneys from patients with autosomal dominant polycystic kidney disease. The evidence suggests that the somatic (point) mutations must either allow transcription of the mutated wild-type allele or block production of polycystin-1 or polycystin-2.

Although complete loss of PKD1 or PKD2 clearly causes massive formation of renal cysts (Table 2), there is also a gene dose effect, since either too little PKD1 (complete absence or haploinsufficiency) or too much PKD1 (transgenic overexpression) causes cyst formation.

The gene for autosomal recessive polycystic kidney disease, PKHD1, has 67 exons and encodes a large 16.2-kb transcript. Many splice variants exist, and several different mutations have been detected throughout the entire coding region. Most mutations predict the translation of a truncated protein (Table 2).

The juvenile nephronophthisis gene, NPH1, has 20 exons and encodes a small 4.5-kb transcript. Seventy to 80 percent of affected patients have homozygous deletions, whereas the remainder are heterozygotes. A variety of inactivating, nonsense, splice-site, and point mutations have been identified (Table 2). The juvenile nephronophthisis gene, NPH1, has 20 exons and encodes a small 4.5-kb transcript. Seventy to 80 percent of affected patients have homozygous deletions, whereas the remainder are heterozygotes. A variety of inactivating, nonsense, splice-site, and point mutations have been identified (Table 2).

Polycystin-1

Polycystin-1 is a large (>460 kD) membrane protein with a long extracellular N-terminal, 11 transmembrane domains, and a short intracellular C-terminal. Its extracellular portion contains structural motifs for binding matrix and cell-membrane proteins in the environment of renal tubular epithelia. The intracellular portion of the protein has many sites for phosphorylation and responses to regulators of signal transduction. Polycystin-1 interacts and forms complexes with many other proteins. The protein is localized to cilia and is missing in patients with autosomal recessive polycystic kidney disease.

**Figure 5. Polycystin-1–Focal Adhesion Complex.**

As shown in Panel A, in normal renal epithelia, polycystin-1 interacts in a multiprotein complex with integrins and focal adhesion proteins, including the focal adhesion kinase (FAK). As shown in Panel B, in epithelia from patients with autosomal dominant polycystic kidney disease, although polycystin–focal-adhesion complexes are formed, they lack FAK. TAL denotes talin, PAX paxillin, VINC vinculin, CAS p130-cas, SRC c-src, TEN tensin, and NPH1 nephrocystin.
er proteins in the plane of the cell membrane and on the intracellular face of the membrane that links the extracellular environment to the intracellular actin cytoskeleton (Fig. 4).

**Polycystin-2**

The PKD2-encoded protein polycystin-2 is a 110-kD membrane protein with six transmembrane domains and intracellular N- and C-terminal domains with structural similarities to voltage-activated L-type calcium and sodium channels. Structural and functional analyses place polycystin-2 in the transient receptor potential family of channel proteins together with the newly identified polycystin-like calcium channels PKDL and PKD2L2. Although polycystin-2 can function as a nonselective cation channel that is permeable to calcium, there is uncertainty whether it functions alone or only when it forms a complex with polycystin-1 at the cell membrane or in the endoplasmic reticulum.

**Fibrocystin**

Although little is known about the large (447-kD) protein involved in autosomal recessive polycystic kidney disease, fibrocystin (also known as polyductin), its structure suggests that it is an integral membrane receptor with extracellular protein-interaction sites and intracellular phosphorylation sites (Fig. 1). Disease-causing mutations of PKHD1 truncate the C-terminal of fibrocystin, removing or inactivating putative signaling sites. Fibrocystin is abundant in fetal-kidney collecting ducts but absent in the kidneys of some patients with autosomal recessive polycystic kidney disease. Taken together, these properties suggest that like polycystin-1, fibrocystin may act as a membrane receptor, interacting with extracellular protein ligands and transducing intracellular signals to the nucleus.

**Nephrocystin**

Unlike the polycystins and fibrocystin, nephrocystin is a wholly intracellular small (83-kD) protein. It binds to focal adhesion proteins, including p130cas and tensin. The polycystins and nephrocystin probably interact with focal-adhesion-complex proteins, in which phosphorylation activates intracellular signaling pathways (Fig. 4). Evidence supports the existence of a central role for the control of polycystin–nephrocystin–adhesion complexes at focal adhesion points in the cell matrix for the regulation of renal tubule geometry.

**Functions of Polycystins**

A wide range of analyses have led to the conclusion that polycystin-1 functions as a membrane receptor, capable of binding and interacting with many proteins, carbohydrates, and lipids and eliciting intracellular responses through phosphorylation pathways and that polycystin-2 acts as a calcium-permeable channel. Polycystin-1 is found at three major renal tubular cell sites: the cell–matrix focal adhesion complex, cell–cell junctions, and the cilium, each of which links the extracellular environment of the cell membrane to the intracellular actin–tubulin cytoskeleton (Fig. 4). Through multiple interactions with other proteins and modifications by phosphorylation, polycystin complexes

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**Table 2. Molecular Mechanisms of Polycystic Kidney Disease.**

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Cause</th>
<th>Reference</th>
<th>Molecular Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant polycystic kidney</td>
<td>Mutation in PKD1</td>
<td>European PK Consortium^7,^75</td>
<td>Polycystin-1 is a membrane mechanoreceptor-like protein that forms multiprotein complexes at focal adhesions, cell–cell junctions, and cilia. Interactions with the extracellular environment lead to intracellular signaling and transcriptional regulation of proteins that regulate renal morphogenesis and differentiation, including control of renal tubule diameter through effects on epithelial-cell proliferation, adhesion, and migration.</td>
</tr>
<tr>
<td>disease</td>
<td>Decrease in functional polycystin-1</td>
<td>Hughes et al. ^76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mochizuki et al. ^4</td>
<td></td>
<td>Polycystin-2 is a nonselective cation, calcium-permeable membrane channel that interacts with the polycystin-1 complex and may regulate transport of polycystin-1 from the endoplasmic reticulum to the plasma membrane.</td>
</tr>
<tr>
<td>Autosomal recessive polycystic kidney</td>
<td>Mutation in PKHD1</td>
<td>Ward et al., ^11</td>
<td>Fibrocystin is a receptor-like membrane protein with putative extracellular-matrix–interaction domains as well as intracellular signaling sites.</td>
</tr>
<tr>
<td>disease</td>
<td>Loss of functional fibrocystin</td>
<td>Hildebrandt et al. ^48</td>
<td></td>
</tr>
<tr>
<td>Juvenile nephronophthisis</td>
<td>Mutation in NPH1</td>
<td>Antignac et al., ^14</td>
<td>Nephrocystin is an intracellular protein that interacts with the focal adhesion complex, the cilium, and tyrosine signaling molecules.</td>
</tr>
<tr>
<td></td>
<td>Loss of functional nephrocystin</td>
<td>Hildebrandt and Otto ^15</td>
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</table>
stimulate intracellular signaling cascades that influence gene transcription. The evidence suggests that the polycystin complex acts as a mechanosensor, receiving signals from the extracellular matrix (by means of focal adhesions), adjacent cells (through cell junctions), and tubule lumen (through cilia), and transduces them into cellular responses that regulate proliferation, adhesion, migration, differentiation, and maturation essential for the control of the diameter of renal tubules and kidney morphogenesis.

DEVELOPMENTAL REGULATION AND PROGRAMMING

Autosomal dominant polycystic kidney disease is a developmental disorder. Multiple renal cysts occur in utero, mice with homozygous targeted disruptions of the pkd1 or pkd2 gene die in utero or perinatally, and many fetal genes, proteins, and functions are expressed in affected patients. Polycystin-1 is predominantly found in basal-membrane focal adhesions of migrating epithelia derived from the ureteric bud. Later in gestation and in the adult kidney, expression of polycystin-1 is down-regulated and restricted to medullary collecting-tubule cells and low levels in adult kidneys. In kidneys from 8- to 16-week-old fetuses, polycystin-1 is predominantly found in basal-membrane focal adhesions of migrating epithelia. Polycystin-1- is important in the regulation of adhesion, migration, and branching elongation of the ureteric bud during renal development. Mutations in PKD1, PKD2, or NPH1 disrupt this finely coordinated process and lead to the formation of cysts.

PROSPECTS FOR PROGNOSIS AND THERAPY

Some genetic factors that influence the rate of progression of autosomal dominant polycystic kidney disease to end-stage renal failure have been identified, including the nature of the inherited mutation. Patients with mutations in PKD2 (type II) have a slower rate of disease progression than patients with mutations in PKD1 (type I), mutations in the 5' portion of PKD1 lead to the early onset of a rapidly progressive disease, and the presence of both PKD1 and PKD2 mutations is predictive of severe disease. Associated conditions such as hypertension also increase the severity of the disease, possibly through effects of modifier genes, as suggested by the earlier onset of end-stage renal failure in patients with autosomal dominant polycystic kidney disease and angiotensin-converting–enzyme deletion polymorphisms. Another accelerator of progression is interstitial fibrosis, whether it is caused by the proliferation of fibroblasts, inflammatory cytokines, toxic and traumatic insults, or dietary additives. The recent availability of rodent models with targeted mutations in pkd1 and pkd2 or with spontaneous mutations syntenic to mutations in NPH3 (Pcy mouse) and PKHD1 (Pck rat) and well-characterized primary and conditionally immortalized renal epithelial cell cultures from normal human fetal and adult nephron segments, as well as cyst lining epithelia from patients with autosomal dominant polycystic kidney disease and autosomal recessive polycystic kidney disease, should speed the development of genetic, pharmacologic, or dietary interventions.

Because autosomal dominant polycystic kidney disease is slowly progressive, there is a window of opportunity to treat the disease by retarding cystic expansion. However, new methods of assessing renal decline, such as monitoring the reduction in the numbers and size of cysts, must be developed and accepted by regulatory agencies. The most promising example of potential therapy is the EGF-receptor tyrosine kinase inhibitors. Treatment of the more rapidly progressing forms of polycystic kidney diseases may present a greater challenge, since treatment will have to occur during the developmental period. In these cases, other tyrosine and serine kinase targets as well as gene-therapy approaches may prove optimal.

REFERENCES

5. Otto EA, Schermer B, Obaza T, et al. Mu-
tations in INVS encoding inverse cause nephropathophysiology type 2, linking renal cystic disease to the function of primary cilia and left-right axis determination. Nat Genet 2003;34:413-20.


