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Invited Review

Polycystic kidney disease and renal injury repair: common pathways, fluid flow, and the function of polycystin-1

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Weimbs T. Polycystic kidney disease and renal injury repair: common pathways, fluid flow, and the function of polycystin-1. *Am J Physiol Renal Physiol* 293: F1423–F1432, 2007. First published August 22. 2007; doi:10.1152/ajprenal.00275.2007.—The root cause for most cases of autosomal-dominant polycystic kidney disease (ADPKD) is mutations in the polycystin-1 (PC1) gene. While PC1 has been implicated in a perplexing variety of protein interactions and signaling pathways, what its normal function is and why its disruption leads to the proliferation of renal epithelial cells are unknown. Recent results suggest that PC1 is involved in mechanotransduction by primary cilia measuring the degree of luminal fluid flow. PC1 has also recently been shown to regulate the mTOR and signal transducers and activators of transcription (STAT) 6 pathways. These two pathways are normally dormant in the healthy kidney but are activated in response to injury and appear to drive a proliferative repair response. This review develops the idea that a critical function of PC1 and primary cilia in the adult kidney may be to sense renal injury by detecting changes in luminal fluid flow and to trigger proliferation. Constitutive activation of these pathways in ADPKD would lead to the futile attempt to repair a nonexisting injury, resulting in cyst growth. The existence of many known cellular and molecular similarities between renal repair and ADPKD supports this model.

mTOR; STAT6; rapamycin; kidney injury and repair; ischemia-reperfusion injury

Polycystic Kidney Disease and Polycystins

AUTOSOMAL-DOMINANT POLYCYSTIC kidney disease (ADPKD) is considered to be the most common life-threatening monogenic inherited disease. The number of people affected in the United States is estimated at over 600,000. To put this into perspective, an estimated 30,000 and 70,000 patients in the United States are affected by cystic fibrosis and sickle cell anemia, respectively. The most significant pathology in ADPKD is the development and growth of thousands of cysts in both kidneys in a progressive manner during adulthood. This results in replacement of normal renal tissue and significant overall growth of the organs. Eventually, most patients experience renal failure, which mandates life-long hemodialysis or kidney transplantation. (For detailed reviews on clinical issues and the pathogenesis of ADPKD, see Refs. 2, 17, 30, 37, 74, 105, 123.)

Mutations in either of two genes, *PKD1* and *PKD2*, are the root cause of ADPKD. Since the discovery of the *PKD* genes over a decade ago, a wealth of information has implicated their protein products, polycystin-1 and -2 (PC1 and PC2), in an impressive variety of mechanisms as discussed below. Despite this, the purpose of the polycystins and why their disruption leads to renal cyst growth are still unclear. ADPKD patients typically only harbor one germline mutation in only one allele of the *PKD1* or *PKD2* gene. The remaining "good" allele is apparently sufficient for all developmental functions that the polycystins may have because patients typically exhibit no developmental abnormalities. Renal cysts in ADPKD are thought to arise after spontaneous, "second-hit" mutations that somatically affect the "good" allele in individual renal epithelial cells, rendering the affected cells devoid of a functional polycystin. Renal cysts probably develop throughout the lifetime of a patient, but the bulk develops in the fully grown adult kidney. This suggests that the polycystins must have a function in the adult kidney. Loss of this function results in aberrant proliferation and cyst growth. The understanding of polycystin function in the adult kidney is complicated by the fact that the polycystins clearly also have developmental functions. *Pkd1*- or *Pkd2*-null mice die in utero and exhibit renal cysts in addition to defects in other organs. Even more complicating are the paradoxical findings that transgenic mice that overexpress PC1 also develop polycystic kidneys (87, 108) and that most cysts in human ADPKD exhibit elevated, and not loss of, PC1 immunoreactivity. Furthermore, in chimeric mice with a mixture of wild-type and *Pkd1*-null renal epithelial cells, both types of cells contributed to the initial growth of cysts (70). While the explanation of all these findings may somehow involve factors such as the biological activity of fragments of PC1 and paracrine communication between epithelial cells during cystogenesis, as discussed below, there is currently no simple, clear-cut model of the role of polycystins in renal cyst formation.

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This poor understanding of the role of the polycystins had made it difficult to devise rational treatment strategies to attempt to slow or prevent the onset of renal failure in ADPKD. Currently, no such treatment exists. However, recent progress in identifying signaling pathways that may be centrally involved in renal cyst growth has caused some cautious optimism that therapeutic approaches may be on the horizon, especially since these pathways can be targeted by existing drugs. This review will focus on two of these signaling pathways, involving mTOR and signal transducers and activators of transcription (STAT) 6, and discuss the possibility that the purpose of the polycystins in the adult kidney may relate to the sensing of renal injury.

Loss of Function of Primary Cilia May Cause Polycystic Kidney Disease

Both PC1 and PC2 have been found to localize, among other places, to the primary cilia of renal epithelial cells (68, 81, 122). Primary cilia are extensions of the apical plasma membrane, which protrude into the lumen of the renal tubules. They are closely related to motile cilia and flagella. However, while the functions of motile cilia on lung epithelial cells and flagella on sperm, for example, are well known, primary cilia in the kidney are nonmotile and their purpose has been historically more mysterious. A recent development has been the discovery that renal primary cilia act as mechanosensors that bend in response to luminal fluid flow, resulting in a transient rise in the intracellular calcium concentration (84–86). Several other proteins whose mutation leads to renal cystic diseases in humans or animals have been found to localize to renal cilia and/or the region surrounding the basal body, one of the centrioles from which primary cilia originate (30, 79, 121, 129). This has led to the current thinking that it is the loss of cilia function that somehow causes a proliferative response in renal epithelial cells, leading to cyst formation.

An important set of questions remains: what are primary cilia sensing and why? If primary cilia solely act as mechanosensors to detect the level of luminal fluid flow, this raises the question as to what the purpose would be. Even under normal conditions, luminal fluid flow along the nephron undergoes dramatic changes. It depends on factors such as the glomerular filtration rate, the degree of water reabsorption, and the diameter of the respective nephron segment. Continuous rhythmic peristaltic contractions in the pelvic wall cause the fluid flow to be intermittent in the medullary kidney structures with a periodicity of a few seconds (97). The glomerular filtration rate itself is not constant but can vary several-fold depending on circulatory demands, fluid and solute input, hormonal changes, etc. These normal fluctuations lead to corresponding changes in proximal tubular fluid and salt reabsorption (29, 98, 113). This phenomenon, glomerulotubular balance, indicates that proximal tubule cells are "well-aware" of the rate of luminal fluid flow and react by adjusting their function, such as sodium reabsorption. This may be achieved by the regulation of membrane trafficking by fluid flow, as reported for the angiotensin receptor (48). While mechanosensation by primary cilia on renal epithelial cells could very well be responsible for mediating these normal responses, it appears highly unlikely that the ups and downs of luminal fluid flow that normally occur in the healthy adult kidney should have any effect on cellular proliferation. Proliferation of renal epithelial cells in the adult kidney is normally extremely low. However, under extreme circumstances, luminal fluid flow may be drastically affected or cease altogether, as, for example, during renal injury. As discussed below, similar signaling pathways appear to be activated both in ADPKD and in response to renal injury. Together with other similarities between these conditions, this may argue in favor of a new idea, namely, that an important function of primary cilia in the kidney may be to sense injury and trigger a proliferative repair program.

It has also been recently discovered that planar cell polarity (PCP) exists among renal tubular epithelial cells (25). In addition to the universal feature of apical-basal polarity among epithelial cells, PCP has been known in many systems, most notably in flies, and refers to a directionality within the plane of the epithelial sheet. It could now be demonstrated for the first time that during early postnatal organ growth, renal tubule epithelial cells align their mitotic spindles along the tubule axis, which results in the insertion of new daughter cells in such a fashion that the tubule lengthens without increasing in width (25). Interestingly, in two rodent models of PKD, this form of PCP was found to be disrupted, which leads to the nearly random alignment of mitotic spindles (25). Consequently, this may lead to the dilation of tubules and may be an initiating factor during the formation of cysts. It is still unknown how tubule epithelial cells determine the correct orientation of their cell division plane. Very plausible suspects are primary cilia, which are bent by the luminal fluid flow along the tubule axis. This possibility would fit well with the fact that the basal bodies/centrosomes, to which primary cilia are connected, duplicate in mitotic cells and become the poles of the spindle apparatus, which determine the mitotic plane. Furthermore, disruption of genes for several proteins that are implicated in PCP pathways in other systems leads to renal cystic diseases in animal models (101). If this hypothesis is correct, this would add another layer of complexity to the function of primary cilia. Not only would they measure the degree of luminal fluid flow and somehow regulate the degree of epithelial proliferation, but they would additionally measure the direction of fluid flow and provide a spatial cue for the establishment of PCP. While a simple increase in tubule epithelial proliferation may primarily lengthen tubules and lead to a larger kidney, the additional disruption of PCP would also result in tubule dilation and ultimately cystogenesis. Conversely, fluid flow-directed cell division would be a useful mechanism not only during renal development but also during the repair of renal injury. Investigating the proposed link between cilia function and PCP may yield fascinating new insights.

Polycystins and Cilia Proteins

As mentioned above, a host of cilia- and basal body-associated proteins has recently been identified. Mutations in these proteins very often lead to renal cyst growth in humans or animals. Besides ADPKD, other human diseases such as Bardet-Biedl syndrome and nephronophthisis involve renal cyst growth and are caused by mutations in genes such as BBS1–12 and NPHP1–6, respectively, whose gene products have often been found to localize to cilia or basal bodies (109, 110, 121). In addition, other affected genes identified in rodents, such as

polaris and Nek8, lead to renal cystic disease but currently have no identified human disease counterpart (109, 110). The functions of most of these cilia proteins are still poorly understood. It is clear, however, that they must play very diverse roles because they include a great variety of proteins, including ion channels, microtubule motors, signaling proteins, and proteins implicated in intraflagellar transport. Since the disruption of any of these diverse proteins leads to renal cyst formation, it appears plausible that their functions eventually converge on one or a few common pathways that are central to the observed changes in proliferation, apoptosis, and differentiation in renal cysts. If this hypothesis is correct, then such a central pathway may be an excellent target for therapeutic intervention.

PC2, also called TRPP2, is affected in 15% of the cases of ADPKD and has been shown to be a calcium-permeable, nonselective cation channel of the TRP channel family (28). PC1, affected in 85% of the ADPKD cases, is an integral membrane protein with a very large extracytoplasmic domain, 11 transmembrane domains, and a COOH-terminal cytoplasmic tail, whose domain structure suggests a potential surface receptor function. PC1 and PC2 can physically interact with each other via binding of their cytoplasmic tails (69, 89). This fact, together with the extremely similar clinical phenotype caused by PC1 and PC2 mutations, strongly suggests that both proteins act together, at least in the kidney. Renal epithelial cells that are null for PC1 lack the normal response to apical fluid flow, namely, a cilia-dependent, temporary rise in intracellular calcium (68). Addition of a blocking PC2 antibody also abolishes the flow response (67). This suggests that PC1 and PC2 may form a heteromeric ion channel involved in ciliary mechanotransduction. It has been estimated, based on electrophysiological measurements, that a single such polycystin channel in each primary cilium would be sufficient for flow sensing, resulting in an intracellular calcium signal (85).

While the existence of such a heteromeric polycystin channel seems well supported, it is very unlikely that ion channel activity fully accounts for the function of the polycystins, particularly of PC1. In addition to PC2, PC1 has been reported to bind to a perplexing variety of cytoplasmic and extracytoplasmic proteins. Extracytoplasmically, PC1 was shown to interact with itself via homophilic interactions of its Ig-like domains (36), with carbohydrates via its C-type lectin domain (118), and with several extracellular matrix proteins (63) and annexin-A5 (64) via its leucine-rich repeats. On its cytoplasmic side, PC1 has been found to interact again with itself by homotypic interaction of its COOH-terminal coiled-coil domain (89); with E-cadherin and α-, β-, and γ-catenin (35); with the regulator of G protein signaling RGS7 (43); with heterotrimeric G proteins (77); with the intermediate filament proteins vimentin, desmin, and cytokeratins K8 and K18 (120); with Siah-1, a protein involved in targeting for proteasome-dependent degradation (45); with the tyrosine-kinase JAK2 (6); with homer-1a/Vesl-1S, a protein implicated in synaptic plasticity (104); with polycystin-L, a relative of polycystin-2 (14); and with the Na^+-K^+-ATPase α-subunit (127). These cytoplasmic interactions involve the ~200-residue-long COOH-terminal cytoplasmic tail of PC1. In addition to affecting these proteins, PC1 has been implicated in the functional regulation of wnt-signaling (44), the activities of the transcription factor AP-1, protein kinase C, Rac-1, Cdc42 (3, 4, 54, 78), STAT1 (6), Akt and PI3-K (7), the regulation of proliferation and apoptosis (6, 8), cell-cell adhesion (36), and cell cycle regulation via the transcription factor Id2 (55).

It is still unclear which of these interactions/regulations is critical for the function of PC1 in the kidney and for mediating cyst growth in ADPKD. It is possible that PC1 may be part of an enormous multiprotein complex that contains all of the above and carries out a multitude of functions at the same time. However, it may be more likely that PC1 has several separate functions. Exactly which protein interaction PC1 engages in may depend on the particular PC1 splice isoform, its subcellular localization, the cell type, or the developmental stage. For example, PC1 has been found to localize to cell-cell junctions (35, 36, 47, 82, 96) and to primary cilia (68, 122). However, some proposed interacting proteins such as E-cadherin, the Na^+-K^+-ATPase, or intermediate filament proteins seem unlikely to be found on cilia. It would therefore seem reasonable that PC1 has at least two distinct functions in renal epithelial cells: one on cell-cell junctions and another on primary cilia. Because of the established strong link between primary cilia and renal cyst growth, it would be tempting to simplify matters by proposing that only disruption of the "cilia function" of PC1 is relevant for renal cystic disease. On the other hand, oversimplification can be dangerous and may lead us to overlook an important mechanism.

PC1 clearly has functions in cell types other than renal epithelial cells because extrarenal pathologies such as intracranial aneurisms and liver cysts occur in ADPKD. Furthermore, cardiac, vascular, and skeletal abnormalities observed in gene knockout studies suggest extrarenal developmental functions of PC1 (11, 46, 62). Recently, placental abnormalities have also been reported in PC1-null animals (1). The finding that only PC2-null animals, but not PC1-null animals, exhibit an organ laterality defect indicates that PC2 can function independently of PC1 (41), at least in the nodal cells that are responsible for laterality determination during early embryonic development.

Despite the likelihood that PC1 has several distinct functions in various tissues, we will focus on discussing the function in renal epithelial cells, which, when disrupted, leads to polycystic kidneys. If this function indeed involves primary cilia, it would be likely that it is a function that is required in the fully developed adult kidney because cilia are present on almost every renal epithelial cell in the adult kidney. Furthermore, whereas renal cysts can clearly already form in the embryonic kidney in polycystic animal models and human cystic diseases, most cysts in ADPKD are thought to develop during adulthood. It seems unlikely that the purpose of PC1 in the adult kidney is simply to prevent renal cyst growth. Rather, PC1 must have a distinct purpose in the adult kidney. But, what is it?

The answer may lie in two signaling pathways that were recently identified to be regulated by PC1. These two signaling pathways involve the kinase mTOR and the transcription factor STAT6, respectively. As if the list of PC1-interacting proteins was not long enough, additional binding partners, namely, tuberin, mTOR, P100, and STAT6, were recently identified, which led to the recognition of the role of PC1 in their regulation (60, 99) as discussed below. Since the same pathways appear to play a role in the normal response of the kidney to injury, we are discussing the idea that the purpose of PC1 in

the adult kidney may be to activate a proliferative renal epithelial repair program in response to injury.

Regulation of mTOR by PC1 and Tuberin

Tuberin, the product of the *TSC2* gene, is mutated in the autosomal-dominant disease tuberous sclerosis complex (TSC), which is characterized by benign tumors in multiple organs, developmental abnormalities, and kidney cysts (5, 32, 51). Tuberin has emerged as a critical regulator of mTOR activity (38, 56, 76). mTOR stimulates the translation of certain messages by phosphorylating regulators of translation initiation and ribosomal function, most notably 4E-BP1 and the p70-S6-kinase (S6K). mTOR activity stimulates cell growth and proliferation and plays a role in the regulation of differentiation. mTOR activity requires the GTP-bound form of the small G protein rheb. The main mechanism of the function of tuberin appears to be to regulate the GTP/GDP status of rheb by virtue of its GAP domain. The GAP activity of tuberin depends on it being in a complex with hamartin, the product of the *TSC1* gene. The tuberin-hamartin complex therefore acts as an inhibitor of mTOR. Disruption of the tuberin-hamartin complex, e.g., after phosphorylation of tuberin by Akt in response to growth factor signaling, leads to relief of this inhibition and therefore mTOR activation.

Recently reported evidence from our laboratory suggests that PC1, via its cytoplasmic tail, can interact, directly or indirectly, with tuberin and mTOR (99). This interaction would appear to normally result in inhibition of mTOR activity because disruption of PC1 (in ADPKD kidneys or a PC1-null mouse model) leads to a high level of mTOR activity in cyst-lining epithelial cells (99). Furthermore, mTOR activity appears to be a major driving force for renal cyst growth because the mTOR inhibitor rapamycin proved to be highly effective in polycystic animal models. Rapamycin is clinically used for immunosuppression in transplant patients. Treatment of the "orpk-rescue" mouse model (with a defect in the gene for the cilia-associated protein polaris) and the "bpk" mouse model (with a defect in the gene for bicaudal-C) with rapamycin resulted in dramatic inhibition of renal cyst growth and preservation of renal function (99). High levels of mTOR activity were found in cyst-lining cells in these animal models, a PC1-null model, and in an additional polycystic mouse model with transgenic overexpression of the "myelin and lymphocyte" protein MAL (99). Independently, two other groups demonstrated that rapamycin is also effective in reducing renal growth in the polycystic kidney rat model Han:SPRD(cy/+) (107, 114). The gene for the novel protein SamCystin is affected in this rat model (13).

Why do all of these diverse genotypes lead to mTOR activation as the common outcome? The function of SamCystin is presently unknown. The function of the mammalian bicaudal-C is also unknown (22), but its relatives in *Drosophila* and *Xenopus* are RNA-binding proteins implicated in the posttranscriptional regulation of gene expression and patterning during early embryonic development (117). Inhibition of bicaudal-C expression was also recently shown to lead to a PKD-like phenotype in the *Xenopus* pronephros (111). Polaris localizes to primary cilia, where it is part of the so-called intraflagellar transport (IFT) particle, and is required for cilia formation (80). MAL is a tetraspan raft-associated proteolipid implicated in apical membrane trafficking in epithelial cells (20, 27, 66). Currently, no known functional connection exists among PC1, polaris, MAL, bicaudal-C, and SamCystin except that manipulation of either gene leads to activation of mTOR and renal cyst growth. This may suggest that the functions of all these proteins eventually converge on the mTOR pathway, possibly via the function of primary cilia, as illustrated in Fig. 1. This would also suggest that mTOR activation may be the common denominator among most or all renal cystic diseases.

A functional link between tuberin and PC1 is also supported by the previous finding that cells that are null for tuberin exhibit a defect in the trafficking of PC1 to the plasma membrane (47). Furthermore, the *TSC2* (tuberin) and *PKD1* (PC1) genes lie immediately adjacent to each other on the human genome in a tail-to-tail orientation separated by only ~60 nucleotides. This synteny is well conserved from mammals to birds and fish (95). While this synteny in itself may be a (incredibly strange) coincidence, it could also suggest a functional linkage, or at least that the expression of both genes may be coregulated. Patients with a contiguous gene syndrome in which both the *PKD1* and *TSC2* genes are affected by a larger deletion exhibit polycystic kidney disease of much earlier onset and severity than patients with *PKD1* mutations alone (12, 94). At first glance, this apparent additive effect might seem to argue against a model in which PC1 and tuberin act together in the same pathway. However, we need to consider the genetics underlying ADPKD and TSC. In both diseases, only one allele of the *PKD1* or *TSC2* genes, respectively, is affected in the germline, and gene inactivation is thought to occur due to loss of heterozygosity by second-hit somatic events affecting the remaining intact allele (90, 93). Heterozygous mice carrying a *Pkd1*-null allele develop no or only late, occasional kidney cysts (46, 61, 62), suggesting that a ~50% reduction of the PC1 expression level is tolerated. However, further reduction of PC1 expression in two different mouse models carrying low-expressing *Pkd1* alleles results in full-blown polycystic kidney disease (39, 53), suggesting that the PC1 expression level can easily become limiting. This is in agreement with PC1 and tuberin acting together in the same pathway: a 50% reduction in the expression levels of both PC1 and tuberin due to a single germline mutation in *PKD*/*TSC*-

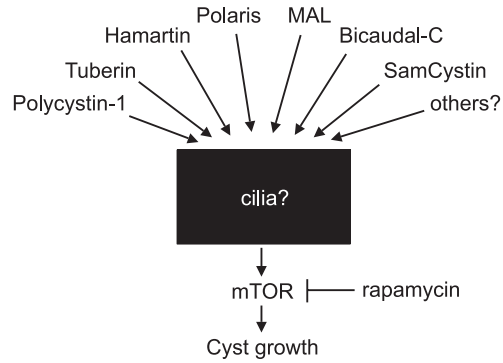

Fig. 1. Converging functions of proteins involved in renal cyst growth. In animals and/or humans, disruption or overexpression of the indicated proteins leads to renal cyst growth. In all of these cases, activation of the mTOR pathway has been demonstrated and/or cyst growth can be inhibited by rapamycin (see text for references). This suggests that the functions of these diverse proteins may converge on the mTOR pathway. MAL, myelin and lymphocyte protein.

contiguous gene syndrome patients would result in the sufficient disruption of their common pathway to lead to cyst growth even in the absence of somatic second-hit mutations. This would explain the observed prenatal onset of renal cyst growth.

Overall, these results are consistent with a model (99, 116) in which PC1 functions to inhibit mTOR by assembling a complex with tuberin and mTOR. The induced proximity of mTOR with its inhibitor tuberin would serve to keep mTOR in its inactive state in the normal adult kidney. It is likely that such a complex would also contain other regulatory components such as rheb and hamartin. Disruption of PC1 in ADPKD would lead to the inability to assemble this inhibitory complex. Tuberin would then become available as a substrate for kinases, such as Akt and RSK1, leading to mTOR activation. In effect, this would hypersensitize epithelial cells in ADPKD to growth factors that activate the PI3-kinase or Erk pathways. EGF-receptor signaling leading to Erk activation has been well documented in human renal cystic diseases and animal models (106).

Does the PC1-Tuberin-mTOR Complex Play a Role in Repair Responses to Renal Injury?

While the normal adult kidney abundantly expresses mTOR, it does not contain significant levels of active mTOR (57, 99). Furthermore, mTOR inhibition by rapamycin, even at very high doses, also has no apparent structural or functional effects on normal kidneys (24, 57, 99) and causes no significant nephrotoxicity in healthy adults (112). All this indicates that mTOR activity is neither present nor needed in the normal adult kidney. If the PC1-tuberin-mTOR complex indeed suppresses mTOR activity in the kidney, what is the purpose of this? Why doesn't the kidney simply turn off the expression of mTOR? The fact that it doesn't suggests that mTOR may need to be activated on short notice under certain circumstances. There are indeed several reported conditions under which mTOR is activated in renal epithelial cells in response to insults. This would suggest that the purpose of the PC1-tuberin-mTOR complex may be to sense these insults and provide the appropriate regulatory response.

Acute renal failure is a serious condition with a very high mortality rate that can be mimicked experimentally by stopping the renal blood supply for some time followed by reperfusion. During such ischemia-reperfusion injury (IRI) experiments, tubular cell death occurs, leading to impairment of renal function. In contrast to many other organs, the kidney has the remarkable capacity to regenerate itself in a process that likely involves the partial dedifferentiation of surviving epithelial cells, proliferation to replace lost cells, and, finally, redifferentiation to re-form functional nephrons (10, 23). Lieberthal et al. (57) reported that the level of the mTOR target phospho-S6K (Thr 412) is dramatically increased in rats during kidney repair after IRI. Furthermore, rapamycin treatment of the animals markedly impaired the recovery of the ischemic kidneys due to inhibition of proliferation and induction of apoptosis. Similarly, in renal transplant patients, immunosuppression with rapamycin has been associated with slower recovery from delayed graft function, again suggesting that active mTOR is required for tubule repair after IRI (67, 102, 103). Altogether, this clearly suggests that mTOR activity is needed as part of a proliferative repair program.

Another way to injure a kidney in animal models is to obstruct the ureter. This leads to the cessation of tubular fluid flow while blood supply to the kidney is maintained. Renal epithelial cells are not directly damaged by this insult but respond to it by starting a process that could be considered a repair program in overdrive. The kidneys increase in size due to proliferation and severe tubular dilation and, in a longer-term process, many cells dedifferentiate to such a degree that they become fibroblastic. This epithelial-to-mesenchymal transition leads to the excessive production of extracellular matrix and renal fibrosis, which is thought to play a role in the progression of chronic kidney disease (58). In this ureteral obstruction model, the actual damage is not caused by the original insult (ureteral ligation) but by the proliferative and profibrotic response of the renal epithelial cells. In this respect, this is the opposite to the IRI model. Interestingly, the renal response to ureteral obstruction can be blunted by treating the animals with rapamycin, which now prevents the damage (119). This suggests again that mTOR activity is essential for this proliferative response to an insult.

Compensatory renal hypertrophy is another trick up the kidney's sleeve to respond to problems. The loss of functioning nephrons results in the growth of remaining tissue as a compensatory measure to restore working capacity. In animal models, removal of one kidney leads to substantial growth of the remaining kidney. In contrast to recovery from ischemic injury, however, this does not involve proliferation but only an increase in the size of renal epithelial cells. Chen et al. (19) found that compensatory renal hypertrophy involves dramatic upregulation of mTOR activity in the kidney. Rapamycin treatment prevents this process. Similar effects of rapamycin on renal hypertrophy associated with proteinuria or renal mass reduction were reported by another group (9). A possibly related process may be the renal hypertrophy that is induced under diabetic conditions and can lead to diabetic nephropathy. Again, renal epithelial cells increase in size in the absence of proliferation. It is unclear whether this is triggered by the increased workload of the kidney or by the overabundance of glucose. Recent studies reported a strong increase in mTOR activity as an early response to the onset of diabetes in rodent models (59, 92). Rapamycin treatment again prevented the renal hypertrophy in these cases.

The overall conclusion from these observations is that mTOR is normally inactive in the kidney unless it is needed in response to insults. In that case, mTOR activation plays an essential role in a proliferative (IRI or ureteral obstruction) or hypertrophic (compensatory hypertrophy or diabetes) response. It is currently unknown by what mechanism mTOR is activated under any of these circumstances. It is tempting to hypothesize that the PC1-tuberin-mTOR complex plays a crucial role. Since PC1 has been implicated in ciliary mechanosensation, an exciting possibility might be that renal injuries can be sensed by changes in tubular fluid flow. During ischemic injury and ureteral obstruction, fluid flow essentially ceases. In contrast, in the conditions that lead to compensatory renal hypertrophy and in diabetes, tubular fluid flow is expected to increase.

Proteolytic Cleavage of PC1 and Function as a Transcriptional Regulator

PC1 has recently been shown to undergo proteolytic processing and to function in an unexpected manner. An extracytoplasmic GPS domain (G protein-coupled receptor proteolytic site) immediately upstream of PC1's first transmembrane domain has been identified based on sequence similarity with GPS domains in several G protein-coupled receptors that undergo cleavage at this site (83). PC1 is indeed cleaved at this site resulting in a large NH_2-terminal fragment that remains noncovalently tethered to the COOH-terminal fragment (88). GPS cleavage of PC1 occurs autocatalytically in the secretory pathway (115). This cleavage event is likely important for the function of PC1 because gene mutations that prevent cleavage cause ADPKD (88). Furthermore, mutated, noncleavable PC1 is unable to elicit in vitro effects such as the induction of tubulogenesis in MDCK cells and the activation of STAT1 (88).

Two groups, including our own, showed independently that PC1 also undergoes cleavage of its cytoplasmic tail, which results in release from the membrane and nuclear translocation (18, 60). This cleavage event was shown to be triggered by the lack of luminal fluid flow after ureteral clamping in mice (18). Our group showed that the cleaved nuclear PC1 tail is also prominent in the cyst-lining epithelium in ADPKD (60). Furthermore, we found that the PC1 tail interacts with the transcription factor STAT6 and the coactivator P100 and that the cleaved PC1 tail strongly stimulates the transcriptional activity of STAT6 (60). In contrast, the membrane-anchored PC1 tail inhibits STAT6 activity. STAT6 and P100 are upregulated in ADPKD cysts and both normally localize to cilia or basal bodies (60). STAT6 translocates from cilia to the nucleus on the loss of apical/luminal fluid flow (60), suggesting that it functions in mechanotransduction from cilia to the nucleus. These results have led us to propose a model in which PC1 normally sequesters STAT6 on cilia, thereby preventing its activation in the healthy kidney. Disruption of luminal fluid flow, e.g., during renal injury, would lead to cleavage of the cytoplasmic tail of PC1, leading to release from cilia, activation of STAT6 and induction of gene expression. Since Chauvet et al. (18) also found high levels of the nuclear PC1 tail in the condensing metanephric mesenchyme and developing tubules in embryonic mouse kidneys, it is tempting to speculate that the onset of luminal fluid flow during renal development may be sensed by cilia and PC1, which would result in the cessation of PC1 cleavage and perhaps provide a signal during the process of epithelial differentiation.

Important open questions are these: what is the protease that cleaves the PC1 tail, how is it regulated? Does cleavage of the cytoplasmic tail depend on prior cleavage at the GPS domain in analogy to the two-step mechanism in many cases of "regulated intramembrane proteolysis" (RIP) in proteins such as notch and the amyloid precursor protein APP (52)? The biggest open question is, What is the purpose of the regulation of STAT6 activity by PC1 in response to lack of fluid flow?

A partial answer to the latter question may have been provided by a study that was done before the discovery of the regulation of STAT6 by PC1 and intended to address a different question. A large body of evidence supports a role of T helper cells (Th) as a pathogenic component in renal IRI (91, 126). Th cells are thought to differentiate into two main phenotypes: Th1 cells, characterized by interferon-γ secretion, and Th2 cells, characterized by secretion of interleukins such as IL-4 and IL-13. The differentiation of Th1 cells depends on STAT4, whereas Th2 cells depend on STAT6. Consequently, STAT4- or STAT6-null mice are deficient in a Th1 or Th2 response, respectively. To identify whether Th1 or Th2 cells are detrimental in renal IRI, Yokota et al. (124) investigated these mice and found that STAT6-null mice exhibit unusually severe renal injury and slow recovery. Surprisingly, however, no clear effect on inflammatory cells such as macrophages and neutrophils, or on proinflammatory cytokines could be detected in STAT6-null mice, which precluded a definite mechanistic explanation (124). It was shown, however, that IL-4-null animals exhibited the same severe response to renal IRI as STAT6-null animals (124). Similarly, another group recently also showed that IL-4-null mice exhibit higher levels of cell damage and severely impaired tubular cell regeneration after renal IRI (65). STAT6 is known to be activated by binding of IL-4 to its receptor (31). Furthermore, in immune cells, the expression of IL-4 is under the control of STAT6, resulting in a positive feedback loop (31). All this suggests that activation of the IL-4/STAT6 pathway provides protection from tissue injury after renal IRI and/or is required for repair of such injury. However, it is unlikely that Th2 cells are entirely responsible.

A more plausible mechanistic explanation of the effect of STAT6 gene deletion on the response to renal ischemic injury takes into account the facts that renal epithelial cells themselves express STAT6, are responsive to IL-4, and that STAT6 is regulated by PC1 depending on luminal fluid flow (60). All this suggests that the IL-4/STAT6 pathway is activated in renal epithelial cells themselves in response to renal injury and that it is required for a proliferative repair response. Similar to the case of mTOR activation above, this again suggests that PC1 functions in triggering such a repair response by detecting changes in luminal fluid flow. A plausible scenario is that Th cells are involved, too, perhaps by communicating with renal epithelial cells via interleukins and/or interferon-γ.

The vast majority of our knowledge of STAT6 function originates from investigations of the immune system. Despite the fact that STAT6 is widely expressed in different tissues, including the kidney (34), very little is known about its role outside of immune cells. The major reported phenotypes of STAT6-null animals are the lack of Th2 differentiation and a defect in immunoglobulin class switching in B cells (40, 100), and these animals appear otherwise normal, suggesting that STAT6 is unlikely to play a role in development or even renal development. Interestingly, just as in the kidney, STAT6 was shown to play a role in repair after IRI in the liver. Treatment with IL-13, which also activates STAT6 via the heterodimeric IL-4/13 receptor, has been shown to inhibit liver injury induced by IRI in a STAT6-dependent fashion (42, 125). However, it was again not investigated which cell type is responsible for the STAT6-dependent effect. An exciting possibility is that the STAT6 pathway plays a general role in proliferative repair processes in tissues and organs that are capable of it.

Similarities Between ADPKD and Renal Repair

The finding that two important pathways, mTOR and STAT6, play a role both in renal injury repair and renal cystic diseases may suggest that a formal proliferative "repair response mechanism" exists dormant in renal epithelial cells and that this mechanism can be triggered rapidly in these otherwise senescent cells. Renal cyst growth in ADPKD and other diseases could then be regarded as being due to the aberrant activation of this repair response mechanism. Indeed, ADPKD has many features in common with a kidney that is responding to ischemic damage or ureteral obstruction. Renal epithelial cells partially dedifferentiate and proliferate in response to ischemic damage, ureteral obstruction, and in ADPKD (2, 10, 23). In addition to a high rate of epithelial proliferation, an increased rate of apoptosis is also observed in these cases. ADPKD kidneys are characterized by severely thickened basement membranes and excessive extracellular matrix deposition (2). Similarly, accumulation of extracellular matrix proteins is observed in ischemic acute renal failure and after ureteral obstruction (10, 26, 58). Matrix metalloproteinases have been implicated in the pathogenesis of both renal IRI and ADPKD (16, 72). Severe tubule dilation occurs after ureteral obstruction just as it does in ADPKD. Importantly, in the case of ureteral obstruction, tubule dilation is not simply due to hydrostatic pressure effects but to proliferation, because mTOR inhibition prevents it (119). As mentioned above, infiltrating phagocytes and lymphocytes are a hallmark of renal IRI and are also observed after ureteral obstruction and, perhaps at a lower magnitude, in human ADPKD and polycystic animal models (91, 128). Progressive fibrosis is observed in polycystic kidney disease, and there is evidence that epithelial cells undergo mesenchymal transition and contribute to the appearance of fibroblasts (73), which resembles the mechanism of fibrosis observed experimentally after ureteral obstruction (58). There are also numerous similarities on the molecular level. For example, clusterin is a glycoprotein that is secreted by renal epithelial cells in response to ischemic injury and excreted with the urine. Similarly, urinary excretion of clusterin is observed in polycystic animals (33). The lectin galectin-3 is upregulated during recovery in ischemic and toxic acute renal failure (71) and also in polycystic kidneys (21). Kidney injury molecule-1 (Kim-1) is expressed in response to renal ischemia and also in polycystic kidneys (50). While the function of Kim-1 is still unknown, it has recently been shown to localize to primary cilia, interact with PC2, and likely play a role in ciliary calcium signaling in response to fluid flow (49). Interestingly, when rats (75) or mice (15) were followed long term (20 or 6 wk, respectively) after ischemic acute kidney injury, prominent tubule dilation and cyst formation were observed, which may suggest that active injury repair can "overshoot" and go on to cyst growth.

Is the Purpose of PC1 and Cilia to Sense Renal Insults, and is ADPKD a Disease of "Futile" Renal Repair?

The above considerations may lead to a unifying model in which an important function of PC1 and primary cilia is to sense the lack of luminal fluid flow associated with renal injury. This "lack-of-flow" signal would then trigger the tail cleavage of PC1, resulting in activation of both mTOR and STAT6 pathways. Together with other signals, such as possibly provided by infiltrating immune cells, this would then trigger a formal, preexisting epithelial program, leading to dedifferentiation and proliferation required for injury repair. In ADPKD, this repair program would be aberrantly activated because of the lack of functional PC1 and/or cilia leading to a futile repair process, resulting in cyst growth (Fig. 2).

This "repair hypothesis" is appealing because it explains why so many different genetic defects all lead to the same outcome, namely, renal cyst formation. If any protein that plays a role in ciliary mechanosensation is mutated, we would expect that consequently the same formal cellular response program is activated. This model would also explain the apparent similarities between renal repair and ADPKD. Clearly, much work lies ahead to test this unifying model.

The identification of the involvement of the mTOR pathway in ADPKD has already led to the start of several clinical trials that will test the possible efficacy of mTOR inhibitors in ADPKD. These include phase II-III trials in Switzerland, Germany, the United States (www.clinicaltrials.gov), and Italy.

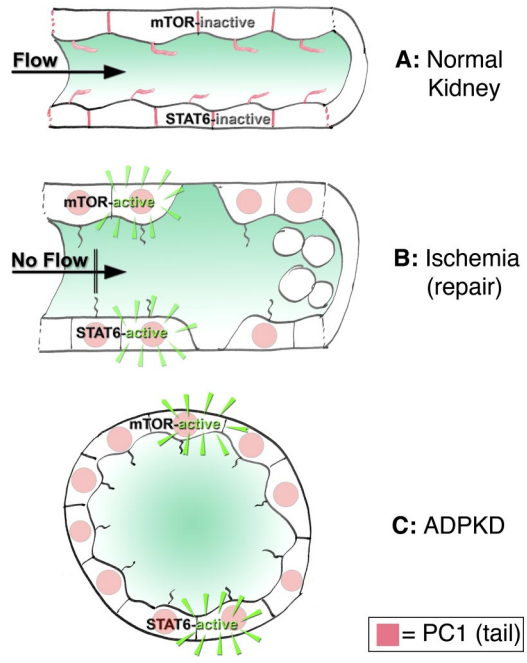

Fig. 2. Model of the role of fluid flow, polycystin-1 (PC1), mTOR, and STAT6 in renal injury repair and autosomal-dominant polycystic kidney disease (ADPKD). *A*: in normal renal tubule epithelial cells, luminal fluid flow stimulates primary cilia and PC1 remains intact and localizes to primary cilia and the lateral plasma membranes (pink). Under those conditions, mTOR and STAT6 activities are suppressed. *B*: ischemia leads to lack of luminal fluid flow and death of some renal epithelial cells, which are shed into the lumen, contributing to further flow obstruction. Lack of ciliary mechanostimulation leads to proteolytic cleavage of the PC1 tail, which translocates to the nucleus (pink). This results in lack of mTOR inhibition, which can now be activated by growth factor signaling. PC1 tail cleavage also results in lack of STAT6 inhibition on cilia. STAT6 can be activated by cytokine signaling and is coactivated by the nuclear PC1 tail. Altogether, this leads to proliferation of epithelial cells to repair the damaged tubule. *C*: in ADPKD, lack of functional membrane/cilia-associated PC1 leads to constitutive activation of the mTOR and STAT6 pathways, resulting in aberrant proliferation and cyst growth.

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REFERENCES

1. **Allen E, Piontek KB, Garrett-Mayer E, Garcia-Gonzalez M, Gorelick KL, Germino GG.** Loss of polycystin-1 or polycystin-2 results in dysregulated apolipoprotein expression in murine tissues via alterations in nuclear hormone receptors. *Hum Mol Genet* 15: 11–21, 2006.
2. **Arnaout MA.** Molecular genetics and pathogenesis of autosomal dominant polycystic kidney disease. *Annu Rev Med* 52: 93–123, 2001.
3. **Arnould T, Kim E, Tsiokas L, Jochimsen F, Gruning W, Chang JD, Walz G.** The polycystic kidney disease 1 gene product mediates protein kinase C alpha-dependent and c-Jun N-terminal kinase-dependent activation of the transcription factor AP-1. *J Biol Chem* 273: 6013–6018, 1998.
4. **Arnould T, Sellin L, Benzing T, Tsiokas L, Cohen HT, Kim E, Walz G.** Cellular activation triggered by the autosomal dominant polycystic kidney disease gene product PKD2. *Mol Cell Biol* 19: 3423–3434, 1999.
5. **Astrinidis A, Henske EP.** Tuberous sclerosis complex: linking growth and energy signaling pathways with human disease. *Oncogene* 24: 7475–7481, 2005.
6. **Bhunia AK, Piontek K, Boletta A, Liu L, Qian F, Xu PN, Germino FJ, Germino GG.** PKD1 induces p21(waf1) and regulation of the cell cycle via direct activation of the JAK-STAT signaling pathway in a process requiring PKD2. *Cell* 109: 157–168, 2002.
7. **Boca M, Distefano G, Qian F, Bhunia AK, Germino GG, Boletta A.** Polycystin-1 induces resistance to apoptosis through the phosphatidylinositol 3-kinase/Akt signaling pathway. *J Am Soc Nephrol* 17: 637–647, 2006.
8. **Boletta A, Qian F, Onuchic LF, Bhunia AK, Phakdeekitcharoen B, Hanaoka K, Guggino W, Monaco L, Germino GG.** Polycystin-1, the gene product of PKD1, induces resistance to apoptosis and spontaneous tubulogenesis in MDCK cells. *Mol Cell* 6: 1267–1273, 2000.
9. **Bonegio RG, Fuhro R, Wang Z, Valeri CR, Andry C, Salant DJ, Lieberthal W.** Rapamycin ameliorates proteinuria-associated tubulointerstitial inflammation and fibrosis in experimental membranous nephropathy. *J Am Soc Nephrol* 16: 2063–2072, 2005.
10. **Bonventre JV.** Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. *J Am Soc Nephrol* 14, *Suppl* 1: S55–S61, 2003.
11. **Boulter C, Mulroy S, Webb S, Fleming S, Brindle K, Sandford R.** Cardiovascular, skeletal, and renal defects in mice with a targeted disruption of the Pkd1 gene. *Proc Natl Acad Sci USA* 98: 12174–12179, 2001.
12. **Brook-Carter PT, Peral B, Ward CJ, Thompson P, Hughes J, Maheshwar MM, Nellist M, Gamble V, Harris PC, Sampson JR.** Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease–a contiguous gene syndrome. *Nat Genet* 8: 328–332, 1994.
13. **Brown JH, Bihoreau MT, Hoffmann S, Kranzlin B, Tychinskaya I, Obermuller N, Podlich D, Boehn SN, Kaisaki PJ, Megel N, Danoy P, Copley RR, Broxholme J, Witzgall R, Lathrop M, Gretz N, Gauguier D.** Missense mutation in sterile alpha motif of novel protein SamCystin is associated with polycystic kidney disease in (cy/+) rat. *J Am Soc Nephrol* 16: 3517–3526, 2005.
14. **Bui-Xuan EF, Li Q, Chen XZ, Boucher CA, Sandford R, Zhou J, Basora N.** More than colocalizing with polycystin-1, polycystin-L is in the centrosome. *Am J Physiol Renal Physiol* 291: F395–F406, 2006.
15. **Burne-Taney MJ, Yokota N, Rabb H.** Persistent renal and extrarenal immune changes after severe ischemic injury. *Kidney Int* 67: 1002–1009, 2005.
16. **Catania JM, Chen G, Parrish AR.** Role of matrix metalloproteinases in renal pathophysiologies. *Am J Physiol Renal Physiol* 292: F905–F911, 2007.
17. **Chapman AB.** Autosomal dominant polycystic kidney disease: time for a change? *J Am Soc Nephrol* 18: 1399–1407, 2007.
18. **Chauvet V, Tian X, Husson H, Grimm DH, Wang T, Hieseberger T, Igarashi P, Bennett AM, Ibraghimov-Beskrovnaya O, Somlo S, Caplan MJ.** Mechanical stimuli induce cleavage and nuclear translocation of the polycystin-1 C terminus. *J Clin Invest* 114: 1433–1443, 2004.
19. **Chen JK, Chen J, Neilson EG, Harris RC.** Role of mammalian target of rapamycin signaling in compensatory renal hypertrophy. *J Am Soc Nephrol* 16: 1384–1391, 2005.
20. **Cheong KH, Zacchetti D, Schneeberger EE, Simons K.** VIP17/MAL, a lipid raft-associated protein, is involved in apical transport in MDCK cells. *Proc Natl Acad Sci USA* 96: 6241–6248, 1999.
21. **Chiu MG, Johnson TM, Woolf AS, Dahm-Vicker EM, Long DA, Guay-Woodford L, Hillman KA, Bawumia S, Venner K, Hughes RC, Poirier F, Winyard PJ.** Galectin-3 associates with the primary cilium and modulates cyst growth in congenital polycystic kidney disease. *Am J Pathol* 169: 1925–1938, 2006.
22. **Cogswell C, Price SJ, Hou X, Guay-Woodford LM, Flaherty L, Bryda EC.** Positional cloning of jcpk/bpk locus of the mouse. *Mamm Genome* 14: 242–249, 2003.
23. **Devarajan P.** Update on mechanisms of ischemic acute kidney injury. *J Am Soc Nephrol* 17: 1503–1520, 2006.
24. **DiJoseph JF, Sharma RN, Chang JY.** The effect of rapamycin on kidney function in the Sprague-Dawley rat. *Transplantation* 53: 507–513, 1992.
25. **Fischer E, Legue E, Doyen A, Nato F, Nicolas JF, Torres V, Yaniv M, Pontoglio M.** Defective planar cell polarity in polycystic kidney disease. *Nat Genet* 38: 21–23, 2006.
26. **Forbes JM, Hewitson TD, Becker GJ, Jones CL.** Ischemic acute renal failure: long-term histology of cell and matrix changes in the rat. *Kidney Int* 57: 2375–2385, 2000.
27. **Frank M, Atanasoski S, Sancho S, Magyar JP, Rulicke T, Schwab ME, Suter U.** Progressive segregation of unmyelinated axons in peripheral nerves, myelin alterations in the CNS, and cyst formation in the kidneys of myelin and lymphocyte protein-overexpressing mice. *J Neurochem* 75: 1927–1939, 2000.
28. **Giamarchi A, Padilla F, Coste B, Raoux M, Crest M, Honore E, Delmas P.** The versatile nature of the calcium-permeable cation channel TRPP2. *EMBO Rep* 7: 787–793, 2006.
29. **Haberle DA, von Baeyer H.** Characteristics of glomerulotubular balance. *Am J Physiol Renal Fluid Electrolyte Physiol* 244: F355–F366, 1983.
30. **Harris PC, Torres VE.** Understanding pathogenic mechanisms in polycystic kidney disease provides clues for therapy. *Curr Opin Nephrol Hypertens* 15: 456–463, 2006.
31. **Hebenstreit D, Wirnsberger G, Horejs-Hoeck J, Duschl A.** Signaling mechanisms, interaction partners, and target genes of STAT6. *Cytokine Growth Factor Rev* 17: 173–188, 2006.
32. **Henske EP.** Tuberous sclerosis and the kidney: from mesenchyme to epithelium, and beyond. *Pediatr Nephrol* 20: 854–857, 2005.
33. **Hidaka S, Kranzlin B, Gretz N, Witzgall R.** Urinary clusterin levels in the rat correlate with the severity of tubular damage and may help to differentiate between glomerular and tubular injuries. *Cell Tissue Res* 310: 289–296, 2002.
34. **Hou J, Schindler U, Henzel WJ, Ho TC, Brasseur M, McKnight SL.** An interleukin-4-induced transcription factor: IL-4 Stat. *Science* 265: 1701–1706, 1994.
35. **Huan Y, van Adelsberg J.** Polycystin-1, the PKD1 gene product, is in a complex containing E- cadherin and the catenins. *J Clin Invest* 104: 1459–1468, 1999.
36. **Ibraghimov-Beskrovnaya O, Bukanov NO, Donohue LC, Dackowski WR, Klinger KW, Landes GM.** Strong homophilic interactions of the Ig-like domains of polycystin-1, the protein product of an autosomal dominant polycystic kidney disease gene, PKD1. *Hum Mol Genet* 9: 1641–1649, 2000.
37. **Igarashi P, Somlo S.** Genetics and pathogenesis of polycystic kidney disease. *J Am Soc Nephrol* 13: 2384–2398, 2002.
38. **Inoki K, Corradetti MN, Guan KL.** Dysregulation of the TSC-mTOR pathway in human disease. *Nat Genet* 37: 19–24, 2005.
39. **Jiang ST, Chiou YY, Wang E, Lin HK, Lin YT, Chi YC, Wang CK, Tang MJ, Li H.** Defining a link with autosomal-dominant polycystic kidney disease in mice with congenitally low expression of Pkd1. *Am J Pathol* 168: 205–220, 2006.
40. **Kaplan MH, Schindler U, Smiley ST, Grusby MJ.** Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity* 4: 313–319, 1996.
41. **Karcher C, Fischer A, Schweickert A, Bitzer E, Horie S, Witzgall R, Blum M.** Lack of a laterality phenotype in Pkd1 knock-out embryos

correlates with absence of polycystin-1 in nodal cilia. *Differentiation* 73: 425–432, 2005.
42. **Ke B, Shen XD, Gao F, Busuttil RW, Kupiec-Weglinski JW.** Interleukin 13 gene transfer in liver ischemia and reperfusion injury: role of Stat6 and TLR4 pathways in cytoprotection. *Hum Gene Ther* 15: 691–698, 2004.
43. **Kim E, Arnould T, Sellin L, Benzing T, Comella N, Kocher O, Tsiokas L, Sukhatme VP, Walz G.** Interaction between RGS7 and polycystin. *Proc Natl Acad Sci USA* 96: 6371–6376, 1999.
44. **Kim E, Arnould T, Sellin LK, Benzing T, Fan MJ, Gruning W, Sokol SY, Drummond I, Walz G.** The polycystic kidney disease 1 gene product modulates Wnt signaling. *J Biol Chem* 274: 4947–4953, 1999.
45. **Kim H, Jeong W, Ahn K, Ahn C, Kang S.** Siah-1 interacts with the intracellular region of polycystin-1 and affects its stability via the ubiquitin-proteasome pathway. *J Am Soc Nephrol* 15: 2042–2049, 2004.
46. **Kim K, Drummond I, Ibraghimov-Beskrovnaya O, Klinger K, Arnaout MA.** Polycystin 1 is required for the structural integrity of blood vessels. *Proc Natl Acad Sci USA* 97: 1731–1736, 2000.
47. **Kleymenova E, Ibraghimov-Beskrovnaya O, Kugoh H, Everitt J, Xu H, Kiguchi K, Landes G, Harris P, Walker C.** Tuberin-dependent membrane localization of polycystin-1: a functional link between polycystic kidney disease and the TSC2 tumor suppressor gene. *Mol Cell* 7: 823–832, 2001.
48. **Kolb RJ, Woost PG, Hopfer U.** Membrane trafficking of angiotensin receptor type-1 and mechanochemical signal transduction in proximal tubule cells. *Hypertension* 44: 352–359, 2004.
49. **Kotsis F, Nitschke R, Boehlke C, Bashkurov M, Walz G, Kuehn EW.** Ciliary calcium signaling is modulated by kidney injury molecule-1 (Kim1). *Pflügers Arch* 453: 819–829, 2007.
50. **Kuehn EW, Park KM, Somlo S, Bonventre JV.** Kidney injury molecule-1 expression in murine polycystic kidney disease. *Am J Physiol Renal Physiol* 283: F1326–F1336, 2002.
51. **Kwiatkowski DJ, Manning BD.** Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways. *Hum Mol Genet* 14, *Spec No* 2: R251–R258, 2005.
52. **Landman N, Kim TW.** Got RI? Presenilin-dependent intramembrane proteolysis in growth factor receptor signaling. *Cytokine Growth Factor Rev* 15: 337–351, 2004.
53. **Lantinga-van Leeuwen IS, Dauwerse JG, Baelde HJ, Leonhard WN, van de Wal A, Ward CJ, Verbeek S, Deruiter MC, Breuning MH, de Heer E, Peters DJ.** Lowering of Pkd1 expression is sufficient to cause polycystic kidney disease. *Hum Mol Genet* 13: 3069–3077, 2004.
54. **Le NH, Van Der Bent P, Huls G, Van De Wetering M, Loghman-Adham M, Ong AC, Calvet JP, Clevers H, Breuning MH, Van Dam H, Peters DJ.** Aberrant polycystin-1 expression results in modification of AP-1 activity, while Wnt signaling remains unaffected. *J Biol Chem* 279: 27472–27481, 2004.
55. **Li X, Luo Y, Starremans PG, McNamara CA, Pei Y, Zhou J.** Polycystin-1 and polycystin-2 regulate the cell cycle through the helix-loop-helix inhibitor Id2. *Nat Cell Biol* 7: 1202–1212, 2005.
56. **Li Y, Corradetti MN, Inoki K, Guan KL.** TSC2: filling the GAP in the mTOR signaling pathway. *Trends Biochem Sci* 29: 32–38, 2004.
57. **Lieberthal W, Fuhro R, Andry CC, Rennke H, Abernathy VE, Koh JS, Valeri R, Levine JS.** Rapamycin impairs recovery from acute renal failure: role of cell-cycle arrest and apoptosis of tubular cells. *Am J Physiol Renal Physiol* 281: F693–F706, 2001.
58. **Liu Y.** Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. *J Am Soc Nephrol* 15: 1–12, 2004.
59. **Lloberas N, Cruzado JM, Franquesa M, Herrero-Fresneda I, Torras J, Alperovich G, Rama I, Vidal A, Grinyo JM.** Mammalian target of rapamycin pathway blockade slows progression of diabetic kidney disease in rats. *J Am Soc Nephrol* 17: 1395–1404, 2006.
60. **Low SH, Vasanth S, Larson CH, Mukherjee S, Sharma N, Kinter MT, Kane ME, Obara T, Weimbs T.** Polycystin-1, STAT6, and P100 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease. *Dev Cell* 10: 57–69, 2006.
61. **Lu W, Fan X, Basora N, Babakhanlou H, Law T, Rifai N, Harris PC, Perez-Atayde AR, Rennke HG, Zhou J.** Late onset of renal and hepatic cysts in Pkd1-targeted heterozygotes. *Nat Genet* 21: 160–161, 1999.
62. **Lu W, Shen X, Pavlova A, Lakkis M, Ward CJ, Pritchard L, Harris PC, Genest DR, Perez-Atayde AR, Zhou J.** Comparison of Pkd1-targeted mutants reveals that loss of polycystin-1 causes cystogenesis and bone defects. *Hum Mol Genet* 10: 2385–2396, 2001.
63. **Malhas AN, Abuknesha RA, Price RG.** Interaction of the leucine-rich repeats of polycystin-1 with extracellular matrix proteins: possible role in cell proliferation. *J Am Soc Nephrol* 13: 19–26, 2002.
64. **Markoff A, Bogdanova N, Knop M, Ruffer C, Kenis H, Lux P, Reutelingsperger C, Todorov V, Dworniczak B, Horst J, Gerke V.** Annexin A5 Interacts with polycystin-1 and interferes with the polycystin-1 stimulated recruitment of E-cadherin into adherens junctions. *J Mol Biol*, 2007.
65. **Marques VP, Goncalves GM, Feitoza CQ, Cenedeze MA, Fernandes Bertocchi AP, Damiao MJ, Pinheiro HS, Antunes Teixeira VP, dos Reis MA, Pacheco-Silva A, Saraiva Camara NO.** Influence of TH1/TH2 switched immune response on renal ischemia-reperfusion injury. *Nephron Exp Nephrol* 104: e48–e56, 2006.
66. **Martin-Belmonte F, Martinez-Menarguez JA, Aranda JF, Ballesta J, de Marco MC, Alonso MA.** MAL regulates clathrin-mediated endocytosis at the apical surface of Madin-Darby canine kidney cells. *J Cell Biol* 163: 155–164, 2003.
67. **McTaggart RA, Gottlieb D, Brooks J, Bacchetti P, Roberts JP, Tomlanovich S, Feng S.** Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. *Am J Transplant* 3: 416–423, 2003.
68. **Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J.** Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 33: 129–137, 2003.
69. **Newby LJ, Streets AJ, Zhao Y, Harris PC, Ward CJ, Ong AC.** Identification, characterization, and localization of a novel kidney polycystin-1-polycystin-2 complex. *J Biol Chem* 277: 20763–20773, 2002.
70. **Nishio S, Hatano M, Nagata M, Horie S, Koike T, Tokuhisa T, Mochizuki T.** Pkd1 regulates immortalized proliferation of renal tubular epithelial cells through p53 induction and JNK activation. *J Clin Invest* 115: 910–918, 2005.
71. **Nishiyama J, Kobayashi S, Ishida A, Nakabayashi I, Tajima O, Miura S, Katayama M, Nogami H.** Up-regulation of galectin-3 in acute renal failure of the rat. *Am J Pathol* 157: 815–823, 2000.
72. **Obermuller N, Morente N, Kranzlin B, Gretz N, Witzgall R.** A possible role for metalloproteinases in renal cyst development. *Am J Physiol Renal Physiol* 280: F540–F550, 2001.
73. **Okada H, Ban S, Nagao S, Takahashi H, Suzuki H, Neilson EG.** Progressive renal fibrosis in murine polycystic kidney disease: an immunohistochemical observation. *Kidney Int* 58: 587–597, 2000.
74. **Ong AC, Harris PC.** Molecular pathogenesis of ADPKD: the polycystin complex gets complex. *Kidney Int* 67: 1234–1247, 2005.
75. **Pagtalunan ME, Olson JL, Tilney NL, Meyer TW.** Late consequences of acute ischemic injury to a solitary kidney. *J Am Soc Nephrol* 10: 366–373, 1999.
76. **Pan D, Dong J, Zhang Y, Gao X.** Tuberous sclerosis complex: from *Drosophila* to human disease. *Trends Cell Biol* 14: 78–85, 2004.
77. **Parnell SC, Magenheimer BS, Maser RL, Rankin CA, Smine A, Okamoto T, Calvet JP.** The polycystic kidney disease-1 protein, polycystin-1, binds and activates heterotrimeric G-proteins in vitro. *Biochem Biophys Res Commun* 251: 625–631, 1998.
78. **Parnell SC, Magenheimer BS, Maser RL, Zien CA, Frischauf AM, Calvet JP.** Polycystin-1 activation of c-Jun N-terminal kinase and AP-1 is mediated by heterotrimeric G proteins. *J Biol Chem* 277: 19566–19572, 2002.
79. **Pazour GJ.** Intraflagellar transport and cilia-dependent renal disease: the ciliary hypothesis of polycystic kidney disease. *J Am Soc Nephrol* 15: 2528–2536, 2004.
80. **Pazour GJ, Dickert BL, Vucica Y, Seeley ES, Rosenbaum JL, Witman GB, Cole DG.** Chlamydomonas IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. *J Cell Biol* 151: 709–718, 2000.
81. **Pazour GJ, San Agustin JT, Follit JA, Rosenbaum JL, Witman GB.** Polycystin-2 localizes to kidney cilia and the ciliary level is elevated in orpk mice with polycystic kidney disease. *Curr Biol* 12: R378–R380, 2002.
82. **Peters DJ, van de Wal A, Spruit L, Saris JJ, Breuning MH, Bruijn JA, de Heer E.** Cellular localization and tissue distribution of polycystin-1. *J Pathol* 188: 439–446, 1999.
83. **Ponting CP, Hofmann K, Bork P.** A latrophilin/CL-1-like GPS domain in polycystin-1. *Curr Biol* 9: R585–588, 1999.
84. **Praetorius HA, Spring KR.** Bending the MDCK cell primary cilium increases intracellular calcium. *J Membr Biol* 184: 71–79, 2001.

85. **Praetorius HA, Spring KR.** Removal of the MDCK cell primary cilium abolishes flow sensing. *J Membr Biol* 191: 69–76, 2003.
86. **Praetorius HA, Spring KR.** The renal cell primary cilium functions as a flow sensor. *Curr Opin Nephrol Hypertens* 12: 517–520, 2003.
87. **Pritchard L, Sloane-Stanley JA, Sharpe JA, Aspinwall R, Lu W, Buckle V, Strmecki L, Walker D, Ward CJ, Alpers CE, Zhou J, Wood WG, Harris PC.** A human PKD1 transgene generates functional polycystin-1 in mice and is associated with a cystic phenotype. *Hum Mol Genet* 9: 2617–2627, 2000.
88. **Qian F, Boletta A, Bhunia AK, Xu H, Liu L, Ahrabi AK, Watnick TJ, Zhou F, Germino GG.** Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations. *Proc Natl Acad Sci USA* 99: 16981–16986, 2002.
89. **Qian F, Germino FJ, Cai Y, Zhang X, Somlo S, Germino GG.** PKD1 interacts with PKD2 through a probable coiled-coil domain. *Nat Genet* 16: 179–183, 1997.
90. **Qian F, Germino GG.** "Mistakes happen": somatic mutation and disease. *Am J Hum Genet* 61: 1000–1005, 1997.
91. **Rodriguez-Iturbe B, Pons H, Herrera-Acosta J, Johnson RJ.** Role of immunocompetent cells in nonimmune renal diseases. *Kidney Int* 59: 1626–1640, 2001.
92. **Sakaguchi M, Isono M, Isshiki K, Sugimoto T, Koya D, Kashiwagi A.** Inhibition of mTOR signaling with rapamycin attenuates renal hypertrophy in the early diabetic mice. *Biochem Biophys Res Commun* 340: 296–301, 2006.
93. **Sampson JR, Harris PC.** The molecular genetics of tuberous sclerosis. *Hum Mol Genet* 3 Spec No: 1477–1480, 1994.
94. **Sampson JR, Maheshwar MM, Aspinwall R, Thompson P, Cheadle JP, Ravine D, Roy S, Haan E, Bernstein J, Harris PC.** Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. *Am J Hum Genet* 61: 843–851, 1997.
95. **Sandford R, Sgotto B, Burn T, Brenner S.** The tuberin (TSC2), autosomal dominant polycystic kidney disease (PKD1), and somatostatin type V receptor (SSTR5) genes form a synteny group in the Fugu genome. *Genomics* 38: 84–86, 1996.
96. **Scheffers MS, van Der Bent P, Prins F, Spruit L, Breuning MH, Litvinov SV, de Heer E, Peters DJ.** Polycystin-1, the product of the polycystic kidney disease 1 gene, co- localizes with desmosomes in MDCK cells. *Hum Mol Genet* 9: 2743–2750, 2000.
97. **Schmidt-Nielsen B, Graves B.** Changes in fluid compartments in hamster renal papilla due to peristalsis in the pelvic wall. *Kidney Int* 22: 613–625, 1982.
98. **Schnermann J, Wahl M, Liebau G, Fischbach H.** Balance between tubular flow rate and net fluid reabsorption in the proximal convolution of the rat kidney. I. Dependency of reabsorptive net fluid flux upon proximal tubular surface area at spontaneous variations of filtration rate. *Pflügers Arch* 304: 90–103, 1968.
99. **Shillingford JM, Murcia NS, Larson CH, Low SH, Hedgepeth R, Brown N, Flask CA, Novick AC, Goldfarb DA, Kramer-Zucker A, Walz G, Piontek KB, Germino GG, Weimbs T.** From the Cover: The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. *Proc Natl Acad Sci USA* 103: 5466–5471, 2006.
100. **Shimoda K, van Deursen J, Sangster MY, Sarawar SR, Carson RT, Tripp RA, Chu C, Quelle FW, Nosaka T, Vignali DA, Doherty PC, Grosveld G, Paul WE, Ihle JN.** Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature* 380: 630–633, 1996.
101. **Simons M, Walz G.** Polycystic kidney disease: cell division without a c(l)ue? *Kidney Int* 70: 854–864, 2006.
102. **Smith KD, Wrenshall LE, Nicosia RF, Pichler R, Marsh CL, Alpers CE, Polissar N, Davis CL.** Delayed graft function and cast nephropathy associated with tacrolimus plus rapamycin use. *J Am Soc Nephrol* 14: 1037–1045, 2003.
103. **Stallone G, Di Paolo S, Schena A, Infante B, Battaglia M, Ditonno P, Gesualdo L, Grandaliano G, Schena FP.** Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. *J Am Soc Nephrol* 15: 228–233, 2004.
104. **Stokely ME, Hwang SY, Hwang JY, Fan B, King MA, Inokuchi K, Koulen P.** Polycystin-1 can interact with homer 1/Vesl-1 in postnatal hippocampal neurons. *J Neurosci Res* 84: 1727–1737, 2006.
105. **Sutters M, Germino GG.** Autosomal dominant polycystic kidney disease: molecular genetics and pathophysiology. *J Lab Clin Med* 141: 91–101, 2003.
106. **Sweeney WE Jr, Avner ED.** Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD). *Cell Tissue Res* 326: 671–685, 2006.
107. **Tao Y, Kim J, Schrier RW, Edelstein CL.** Rapamycin markedly slows disease progression in a rat model of polycystic kidney disease. *J Am Soc Nephrol* 16: 46–51, 2005.
108. **Thivierge C, Kurbegovic A, Couillard M, Guillaume R, Cote O, Trudel M.** Overexpression of PKD1 causes polycystic kidney disease. *Mol Cell Biol* 26: 1538–1548, 2006.
109. **Torres VE, Harris PC.** Polycystic kidney disease: genes, proteins, animal models, disease mechanisms and therapeutic opportunities. *J Intern Med* 261: 17–31, 2007.
110. **Torres VE, Harris PC, Pirson Y.** Autosomal dominant polycystic kidney disease. *Lancet* 369: 1287–1301, 2007.
111. **Tran U, Pickney LM, Özpolat BD, Wessely O.** *Xenopus*bicaudal-C is required for the differentiation of the amphibian pronephros. *Dev Biol* 307: 152–164, 2007.
112. **Vasquez EM.** Sirolimus: a new agent for prevention of renal allograft rejection. *Am J Health Syst Pharm* 57: 437–448, 2000.
113. **Wahl M, Liebau G, Fischbach H, Schnermann J.** Balance between tubular flow rate and net fluid reabsorption in the proximal convolution of the rat kidney. II. Reabsorptive characteristics during constriction of the renal artery. *Pflügers Arch* 304: 297–314, 1968.
114. **Wahl PR, Serra AL, Le Hir M, Molle KD, Hall MN, Wuthrich RP.** Inhibition of mTOR with sirolimus slows disease progression in Han: SPRD rats with autosomal dominant polycystic kidney disease (ADPKD). *Nephrol Dial Transplant* 21: 598–604, 2006.
115. **Wei W, Hackmann K, Xu H, Germino G, Qian F.** Characterization of cis-autoproteolysis of polycystin-1, the product of human polycystic kidney disease 1 gene. *J Biol Chem* 282: 21729–21737, 2007.
116. **Weimbs T.** Regulation of mTOR by polycystin-1: is polycystic kidney disease a case of futile repair? *Cell Cycle* 5: 2425–2429, 2006.
117. **Wessely O, Tran U, Zakin L, De Robertis EM.** Identification and expression of the mammalian homologue of bicaudal-C. *Mech Dev* 101: 267–270, 2001.
118. **Weston BS, Bagneris C, Price RG, Stirling JL.** The polycystin-1 C-type lectin domain binds carbohydrate in a calcium- dependent manner, and interacts with extracellular matrix proteins in vitro. *Biochim Biophys Acta* 1536: 161–176, 2001.
119. **Wu MJ, Wen MC, Chiu YT, Chiou YY, Shu KH, Tang MJ.** Rapamycin attenuates unilateral ureteral obstruction-induced renal fibrosis. *Kidney Int* 69: 2029–2036, 2006.
120. **Xu GM, Sikaneta T, Sullivan BM, Zhang Q, Andreucci M, Stehle T, Drummond I, Arnaout MA.** Polycystin-1 interacts with intermediate filaments. *J Biol Chem* 276: 46544–46552, 2001.
121. **Yoder BK.** Role of primary cilia in the pathogenesis of polycystic kidney disease. *J Am Soc Nephrol* 18: 1381–1388, 2007.
122. **Yoder BK, Hou X, Guay-Woodford LM.** The polycystic kidney disease proteins, polycystin-1, polycystin-2, polaris, and cystin, are co-localized in renal cilia. *J Am Soc Nephrol* 13: 2508–2516, 2002.
123. **Yoder BK, Mulroy S, Eustace H, Boucher C, Sandford R.** Molecular pathogenesis of autosomal dominant polycystic kidney disease. *Expert Rev Mol Med* 8: 1–22, 2006.
124. **Yokota N, Burne-Taney M, Racusen L, Rabb H.** Contrasting roles for STAT4 and STAT6 signal transduction pathways in murine renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol* 285: F319–F325, 2003.
125. **Yoshidome H, Kato A, Miyazaki M, Edwards MJ, Lentsch AB.** IL-13 activates STAT6 and inhibits liver injury induced by ischemia/reperfusion. *Am J Pathol* 155: 1059–1064, 1999.
126. **Ysebaert DK, De Greef KE, De Beuf A, Van Rompay AR, Vercauteren S, Persy VP, De Broe ME.** T cells as mediators in renal ischemia/reperfusion injury. *Kidney Int* 66: 491–496, 2004.
127. **Zatti A, Chauvet V, Rajendran V, Kimura T, Pagel P, Caplan MJ.** The C-terminal tail of the polycystin-1 protein interacts with the Na,K-ATPase alpha-subunit. *Mol Biol Cell* 16: 5087–5093, 2005.
128. **Zeier M, Fehrenbach P, Geberth S, Mohring K, Waldherr R, Ritz E.** Renal histology in polycystic kidney disease with incipient and advanced renal failure. *Kidney Int* 42: 1259–1265, 1992.
129. **Zhang Q, Taulman PD, Yoder BK.** Cystic kidney diseases: all roads lead to the cilium. *Physiology (Bethesda)* 19: 225–230, 2004.