HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2018 April 16.

Published in final edited form as:

Nat Rev Nephrol. 2015 September ; 11(9): 515–534. doi:10.1038/nrneph.2015.46.

Unexpected relevance of the hallmarks of cancer to the pathogenesis of polycystic kidney disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a progressive inherited disorder in which renal tissue is gradually replaced with fluid-filled cysts, giving rise to chronic kidney disease (CKD) and progressive loss of renal function. ADPKD is also associated with liver ductal cysts, hypertension, chronic pain and extrarenal problems such as cerebral aneurysms. Intriguingly, improved understanding of the signalling and pathological derangements characteristic of ADPKD has revealed marked similarities to those of solid tumours, even though the gross presentation of tumours and the greater morbidity and mortality associated with tumour invasion and metastasis would initially suggest an entirely different disease processes. The commonalities between ADPKD and cancer are provocative, particularly in the context of recent preclinical and clinical studies of ADPKD that have shown promise with drugs that were originally developed for cancer. The potential therapeutic benefit of such repurposing has led us to review in detail the pathological features of ADPKD through the lens of the defined, classic hallmarks of cancer. In addition, we have evaluated features typical of ADPKD, and determined

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Competing interests:
The authors declare no competing interests

Contributions.
T.S.-N., D.M.G., A.S.N. and E.A.G. researched data for the article. T.S.-N., D.M.G., and E.A.G. wrote the article. T.B. and A.S.N. contributed to the discussion and helped edit the manuscript for submission.

whether evidence supports the presence of such features in cancer cells. This analysis, which places pathological processes in the context of defined signalling pathways and approved signalling inhibitors, highlights potential avenues for further research and therapeutic exploitation in both diseases.

Introduction

ADPKD is the most common inherited renal pathology. It affects approximately 1 in 500 individuals (~600,000 individuals in the USA alone) and poses a substantial burden to public health. ADPKD is caused by mutations in *PKD1* and *PKD2* (accounting for 85% and 15% of cases, respectively). *PKD1* and *PKD2* encode polycystin 1 and polycystin 2, which are large transmembrane proteins that heterodimerize at cell cilia and elsewhere in the cell, and affect multiple downstream signalling proteins. Affected patients typically experience hypertension and other cardiovascular symptoms commencing in their 20s, and develop an increasing burden of fluid-filled renal cysts by middle age, culminating in end-stage renal disease (ESRD) and the need for dialysis or transplantation [1]. Although ADPKD is associated with significant morbidity, with appropriate clinical management, it is associated with limited mortality. By contrast, cancers can be hereditary, but are more often thought to be sporadic (although this notion might change with ongoing extensive use of next-generation sequencing methods to assess rare or low penetrance predisposition variants), and initiates following mutation of any one of over 100 driver oncogenes or tumour suppressors [2]. The prevalence of cancer is much greater than that of ADPKD, as is the associated mortality: approximately 40% of the population will be diagnosed with some form of cancer in their lifetime, and 34% of these individuals will die within 5 years of diagnosis [3], typically owing to the invasion and metastasis of solid.

The many differences between the presentations and clinical management of ADPKD and cancer have generally resulted in the two diseases being considered separately, by discrete research communities that rarely interact. As discussed below, ADPKD does not predispose to cancer development. However, 25 years ago, the qualitative similarities between these diseases had sparked Jared Grantham to propose that ADPKD might be a “neoplasia in disguise” [4]. On the basis of accumulated insights from the past two decades of investigation, it has become increasingly clear that gross differences in disease presentation (Table 1) obscure extensive similarities between ADPKD and solid tumours at the microscopic and molecular level (Figure 1). Ideally, a comparison of the two diseases might suggest ways in which therapies developed for one disease might be applied to the other. This last point is of particular value for ADPKD, for which few therapeutic options to slow disease progression are available. In spite of this great therapeutic need, the biotechnology and pharmaceutical industry has not prioritized the development of treatments specifically for ADPKD, probably because the process of bringing a new drug forward from basic research discovery through preclinical and clinical testing and finally to regulatory approval takes years and is estimated to cost approximately US$2–3 billion [5–7] providing a strong financial incentive to concentrate drug development efforts on diseases such as cancer, which affect much larger groups of patients. Better understanding of the convergences between critical processes in ADPKD and cancer would support the more efficient

repurposing of cancer therapeutics for ADPKD, a process that has already shown some promise in preclinical studies [8–15], although the outcomes of some clinical studies have been disappointing [11, 12]. Likewise, rigorous comparison of the signalling defects in ADPKD that might also affect cancer could also benefit cancer treatment, by identifying some of the molecular players that regulate the aggressiveness of metastatic disease. In the focused comparison below, space constraints have limited discussion of the pathological (particularly extra-renal) and mechanistic features of ADPKD; however, excellent reviews on these topics are available elsewhere [1, 16–19].

ADPKD and the hallmarks of cancer

In their influential perspective articles published in in 2000 and 2011, Hanahan and Weinberg [20, 21] proposed a set of changes in cellular process that constituted essential properties or “hallmarks” of cancer. These hallmarks were defined as the following sustained proliferative signalling; evasion of growth suppressors; resistance to cell death; replicative immortality; induction of angiogenesis; deregulation of cellular energetics; avoidance of immune destruction; tumour-promoting inflammation; genomic instability and mutation; and activation of invasion and metastasis. For over a decade, the circular figure representing these hallmarks has been a ubiquitous presence in presentations on cancer biology, to emphasize the distinctive features of the disease. However, over the same period, increased understanding of the molecular events that give rise to other pathological conditions, including ADPKD, has diminished the idea that cancer is entirely distinct as a disease. Close assessment of the processes and underlying signalling pathways involved in ADPKD, show that features of this disease align surprisingly well with the defined hallmarks of cancer, although some key differences exist (Figure 1, Table 2). Below, the pathological features of ADPKD are described according to the ten classic hallmarks of cancer.

Sustained proliferative signalling

Proliferative signalling typically involves cascades that are initiated by transmembrane receptor tyrosine kinases (RTKs) that activate cytoplasmic kinases, which in turn induce activity of the ribosomal machinery for protein synthesis and the transcription of genes that support cell growth and the cell cycle. In tumours, this signalling is often abnormally induced by somatic mutations that directly or indirectly activate RTKs and their effectors, and is sustained by autocrine and paracrine signals in reciprocal communication with the tumour microenvironment [21]. In ADPKD, the process of cyst generation requires proliferative expansion of the epithelial lining of the collecting duct or renal tubules [22], although this process is much slower than the proliferative expansion of tumours. Direct measurement of proliferation in early cysts or dilated tubules from human ADPKD specimens [23] and some mouse models of sporadic ADPKD with use of the proliferation markers Ki-67 or BrdU indicate that levels of cell proliferation are typically around 2–3%[24]. Nevertheless, activation of pro-proliferative signalling pathways involving the RTKs EGFR/ErbB1 and HER2/ErbB2 [25, 26], as well as downstream effectors such as B-RAF, ERK [27, 28], mTOR, AKT [29, 30], SRC [10] and others [31] have been identified, in association with ADPKD. In addition, increased transcription of genes such as *MYC, c-*

FOS, and genes that encode growth factors that are strongly associated with proliferation, has long been appreciated to be a feature of ADPKD [32, 33].

Several lines of evidence indicate that the increased proliferation and activation of these signalling proteins is important to the pathological presentation of ADPKD.. First, inhibitors of many of these pro-proliferative signalling proteins ([8, 10, 25–31]) or direct inhibition of proteins required for cell cycle functioning, such as CDK1 [9], cause a reduction in cyst growth leading to improved kidney function in preclinical rodent models. Second, transgenic expression of some of these genes, such as *MYC*, is sufficient to drive cystogenesis [34]. Third, the severity of cyst formation is increased if *PKD1* is lost before postnatal day 13, whereas, sporadic onset of a slowly progressive disease is induced by inactivation of *PKD1* after day 14, accompanying a change from higher to lower levels of basal proliferation in renal epithelial cells [24, 35]. Fourth, cyst formation becomes more rapid following late inactivation of *PKD1* if kidneys are injured, which stimulates cell proliferation [24, 36–38].

Of note, although increased rates of proliferation are an obvious characteristic of the developing kidney and of repair following kidney injury, additional elements associated with loss of *PKD1* at early time points or at later time points in association with kidney injury might contribute to the observed rapid progression of ADPKD in these models. For example, the renal gene expression profile differs considerably before and after postnatal day 13, with differences extending beyond the expression of pro-proliferative genes [35] to genes that regulate epithelial cell polarity and cell differentiation, inflammation, and extracellular matrix (ECM) composition, which have been shown in other contexts to also have a role in cystogenesis, as is discussed below.

In addition to cell-intrinsic changes that support proliferation, and again like cancer, ADPKD is associated with induction of microenvironmental changes that enhance aggressive cell growth. In cancer, remodelling of the ECM occurs as a result of signalling between nascent tumours and adjacent stromal cells, resulting in altered morphological constraints, increased rigidity, and the provision of ligands for integrins and other transmembrane proteins that induce pro-proliferative signalling pathways [21, 39, 40]. In ADPKD, fibrotic remodelling of the ECM accompanies cyst expansion and contributes to progressively declining renal function. The degree of fibrosis has been identified as the most important manifestation associated with progression to ESRD [41]. Typical fibrotic changes are found in both ADPKD and cancer, including changes in matrix composition (such as increased levels of collagens, matrix metalloproteinases, plasminogen activator inhibitor-1 and transforming growth factor-β [TGF-β]) [41]. The matricellular protein periostin, which is associated with fibrotic conditions and is important for progression in kidney and other cancers [42], is upregulated in cystic tissue, and promoted fibrosis, epithelial cell proliferation and disease progression in a mouse model of PKD [43]. One interesting study from 2014 found that integrins, upregulated in cystic renal tissue, were necessary for early cyst development in *Pkd1*-deficient mice; genetic inactivation of integrin-β1 was sufficient to dramatically inhibit *Pkd1*-dependent cystogenesis [44]. A number of additional mechanisms that have been implicated in ADPKD-associated fibrotic remodelling include interstitial inflammation, impaired function of the primary cilium [45], aberrant signalling pathways of the cystic epithelium as well as vascular remodelling and hypoxia [41].

Evasion of growth suppressors

Cancer cells often inactivate tumour suppressor genes that negatively regulate cell proliferation. These factors include the commonly targeted p53 and Rb, which control cell cycle checkpoints, and others such as NF2, LKB1, and Hippo/LATS, which mediate 'contact inhibition', a mechanism crucial to maintain tissue integrity and prevent inappropriate growth stimuli [21]. Downstream transducers of these tumour suppressors include cell cycle inhibitors such as p21/WAF1 (*CDKN1A*) and p16 (*CDKN2A*), and transcriptional factors including YAP and TAZ that limit cellular growth.

An increasing body of evidence indicates that intact polycystin 1 positively regulates the activity of these growth-restraining proteins via multiple avenues. Expression of p53 is downregulated in cells from *Pkd1*$^{-/-}$ mice [46]. Polycystin 1 inhibits expression of the sirtuin SIRT1, a deacetylase. In *Pkd1* mutant mice, SIRT1 deacetylates Rb, leading to its phosphorylation, which promotes cystic epithelial cell proliferation, and also deacetylates p53, thereby blocking apoptosis [47]. Rb-dependent growth inhibition depends in part on sequestration of the transcription factor E2F; *Pkd1* inactivation upregulates the helix-loop-helix factor transcription regulator Id2, which binds to Rb to release E2F and to induce proliferation, and inhibit expression of p21 [48]. Conversely, the interaction between wild-type polycystin 1 and polycystin 2 can activate the JAK–STAT pathway to upregulate p21, causing cell cycle arrest [49]. However, some models of ADPKD have yielded conflicting data as to whether or not p21 is downregulated in cyst development [50, 51]. Although p16 (*CDKN2A*) is typically also targeted in the deregulated growth of cancer cells, a role for p16 has not been investigated extensively in ADPKD.

Interestingly, *PKD1* and the tuberous sclerosis complex 2 (*TSC2*) tumour suppressor gene [52] are located immediately adjacent to each other on chromosome 16p13.3; consequentially, substantial deletions in that region can simultaneously affect both genes. The resulting TSC2/PKD1 contiguous gene syndrome is characterized by severe early-onset PKD in addition to TSC phenotypes, which include non-malignant tumours that affect the brain, kidney, skin, and other tissues, as well as intellectual deficiencies and seizures [53]. However, renal cysts are also a frequent manifestation of TSC resulting from isolated *TSC2* gene disruptions. Of note, the TSC1/TSC2 heterodimer negatively regulates Rheb, which controls the activity of mTOR. *TSC2* mutations therefore result in activation of mTOR signalling; likewise, mutation of polycystins also activates mTOR. These similarities allow for synergistic interactions between loss of *TSC2* and *PKD1* in cystogenesis ([29] [54]).

Several studies over the past 5 years have suggested that loss of inhibition of the tumour suppressor LKB1, which localizes in part to the primary cilium and is important for suppressing mTOR and limiting cell size, is an important feature in ADPKD [55, 56]. The tumour suppressor Hippo (also known as MST1/2) was first linked to ADPKD by the discovery that mice lacking Taz develop polycystic kidneys [57], and by studies addressing the role of deregulated Taz/Yap activity in other forms of cystic kidney disease [58]. Hippo signals through the intermediary proteins Lats to restrain pro-proliferative transcription factors including Taz and Yap [59], and to inhibit MDM2, thus post-translationally stabilizing p53. Hippo activity is induced by numerous stimuli associated with cell–cell and cell–matrix adhesion, and in 2014 was shown to be induced by cytokinesis failure resulting

in tetraploidy [60]. It is likely that more connections between ADPKD and altered tumour suppressor pathways will be identified.

Resisting cell death

Apoptosis, autophagy and necrosis represent three forms of cell death that have a distinct impact on cancer. Apoptosis provides an important barrier to cancer development that is invariably circumvented during tumour progression. An ‘intrinsic’ apoptosis pathway that involves a balance between pro-apoptotic BAX and anti-apoptotic XIAP and Bcl-2 is often tipped in favour of anti-apoptotic pathways in cancer [61]. An ‘extrinsic’ apoptosis pathway, which involves cell-surface death receptors and signalling via is also reprogrammed [62]. Autophagy, which describes a process of cell degradation that can lead to recycling of cellular components, has a more nuanced action that can mediate either tumour cell survival or cell death, depending on the physiological state of the cell [63]. Necrotic cell death [64, 65] also has an ambiguous role; the release of proinflammatory and regulatory factors, which often accompanies necrotic cell death, can trigger cancer growth to a greater extent than it reduces tumour load, in part by recruiting immune cells that release cytokines within the tumour environment.

To the extent these processes have been studied in ADPKD, marked differences to cancer cells are evident. Only low levels of apoptosis are typically observed during renal cyst development [66], and as noted above, some signalling changes associated with cystogenesis incapacitate the pro-apoptotic signalling function of p53 [47]. However, the basal rate of apoptosis in cells lining epithelial cysts is higher than in normal epithelia [67], and apoptosis most likely contributes to the loss of renal tissue and function [68], albeit over a long time period. Strikingly, genetic depletion of the anti-apoptotic regulator Bcl-2 is sufficient to induce aggressive development of renal cysts in mice [69]. Although some evidence suggests that loss of Bcl-2 might induce cyst growth through a different mechanism than that induced by loss of *Pkd1* [70], other studies have shown that loss of polycystin upregulates the JNK-dependent apoptosis pathway and downregulates Bcl-2, indicating a common [71]. Further, inhibition of the apoptotic ‘executioner’ caspases slowed disease progression in mice with PKD [72], compatible with a role of apoptosis in promoting cystogenesis. On the other hand, a 2013 study found that a Smac-mimetic specifically targeted to the cystic epithelium increased apoptosis in these cells and slowed cystogenesis while preserving renal function [66]. These findings emphasize the importance of discriminating between direct effects on targeted cell populations versus global effects within the renal parenchyma [66].

The exact mechanism by which deregulated apoptosis contributes to cyst formation is a subject of active discussion [67]. Deregulated apoptosis plausibly drives cystic remodelling of renal tissue not in isolation but rather in cooperation with increased proliferation of tubular cells with disrupted planar cell polarity (PCP) and disoriented mitotic spindles, as is seen following renal injury [37]. Whether apoptotic cells activate neighbouring cells to proliferate, or whether proliferation triggers apoptosis directly, however, is unclear. In this context, further studies would be helpful to differentiate whether apoptosis is the initial event in the destruction of renal architecture and to better define the mechanisms driving apoptosis in pre-cystic tissue. It is also likely that the role of apoptosis is more nuanced than initial

observations suggest, and provides some benefits. For example, apoptosis protects against DNA damage, which has been associated with polycystin mutations, and might help by providing a natural barrier to malignant transformation in ADPKD (discussed below). Finally, Piontek *et al.* who found differences in rate of cyst formation depending on whether Pkd1 was lost before or after postnatal day 13, found no major differences in the rate of apoptosis in developing kidneys and kidneys from older animals, suggesting that apoptosis is not an essential driver of the rate of cystogenesis [36].

Cell death can also result from increased autophagy and necrosis. Interestingly, Boletta and colleagues found that unlike renal cells from wild-type mice, cells from *Pkd1*$^{-/-}$ mice that had been deprived of glucose did not activate autophagy, but rather manifested an increased apoptotic response. Rapamycin treatment of these cells partially restored autophagy and increased cell survival after glucose deprivation, implicating activation of the mTOR pathway [56]. Other studies have provided further support for a role for autophagy in ADPKD, showing a link between autophagy and ciliogenesis (discussed further below as an important determinant of ADPKD) [73–75]. A more systematic analysis of autophagy in ADPKD is certainly worth undertaking.

To our knowledge, the process of necrosis and necrosis-related signalling has not been directly addressed in ADPKD. The clinical presentation of ADPKD in early stages of cystic growth is not indicative of a substantial role for necrosis. However, the proinflammatory cytokine TNF, which is typically associated with necrosis, is commonly found at elevated levels in cystic fluid, contributes to the mislocalization of polycystin 2, and promotes cystogenesis [76]. A TNF inhibitor slowed disease development in a mouse model of PKD [76], although was less effective in the context of established disease. More work to investigate signalling pathways in ADPKD that are related to the increasingly well-defined necrotic regulatory pathways is merited.

Enabling replicative immortality

Cellular senescence, and the linked phenomenon of replicative crisis limit the replicative potential of normal cells, and must be overcome to allow neoplastic expansion. Senescence can be triggered by excessive signalling by oncogenes such as RAS, which triggers cell checkpoint programmes [77], and by shortening of telomeres beyond a critical limit, leading to chromosomal defects [78]. Tumours circumvent cellular senescence cues by a variety of strategies, including removal of Rb function and upregulating telomerase. Loss of the activity of proteins such as sirtuins which regulate ageing by governing metabolic activity [79], might also contribute to replicative limits; of note, sirtuins are upregulated in tumours [80].

To our knowledge, telomerase expression or shortening of telomeres has not been examined in ADPKD-associated cyst epithelial cells. However, intriguing hints indicate that changes in replicative limits are involved in this disease. Strikingly, one study found that replicative crisis was markedly delayed in cultured mouse embryonic fibroblasts (MEFs) from *Pkd1*$^{-/-}$ mice compared to MEFs from wild-type mice (with replicative crisis occurring at >30 passages versus 13, respectively). This delay in replicative crisis was associated with a significant delay in the upregulation of JNK, p38, and p53 signalling [46]. Oncogenic

signalling pathways, including activation of RAS and its effectors [81–83], are prevalent in ADPKD and contribute to cystogenesis, suggesting that triggers that induce senescence have been removed [45]. As noted above, sirtuins are upregulated in ADPKD epithelial tissue, paralleling findings from immortalized cancer cells. Moreover sirtuin inhibition limits cystogenesis [47].

Intriguingly, mutation of the von Hippel–Lindau gene (*VHL*), as discussed further below, is a common precursor to the development of renal cell carcinomas (RCCs) and renal cysts in humans [84], and causes renal cystogenesis but not RCC in mice [85]. Interestingly, a 2014 study recapitulated the hallmarks of clear cell RCC in mice by generating mice deficient in both the *VHL* and BRCA1-associated protein-1 (*BAP*) genes, which in mice are located on different chromosomes as opposed to in humans where both are found on chromosome 3p [86]. Mice with inactivated *Bap1* developed simple cysts, atypical cysts and neoplastic nodules, with increased Ki-67 and carbonic anhydrase IX staining, supporting the notion that co-deletion of *VHL* and *Bap1* in at least one allele is important for the pathogenesis of clear cell RCC, although the nature of the genetic interaction is not yet understood. A study of the immediate consequences of *VHL* inactivation in mice found that *Vhl* deletion led to a senescence phenotype that was mediated through Rb, which needed to be overcome for cell viability [87]; other studies have shown that intact VHL limits longevity in *Caenorhabditis elegans* [88, 89]. Together, these findings suggest that investigation of immortality controls in ADPKD is warranted.

Angiogenesis

During cancer development, a so-called ‘angiogenic switch’ is almost always activated, resulting in the formation of new, albeit typically aberrant vessels to sustain neoplastic tumour growth. Angiogenesis is supported by an unbalanced mix of proangiogenic signals, including contributions from the tumour cell (including VEGF signalling), from pericytes associated with the neovasculature, and from infiltrating cells of the innate immune system (including macrophages, neutrophils, mast cells and myeloid progenitors) [21].

The vascular system is of considerable importance in ADPKD, not only because of the role of pro-angiogenic signalling in the cystic kidney, but also because the clinical presentation of this disease involves hypertension and a tendency for aortic dissection and cerebral aneurysms [90]. In ADPKD, a rich network of abnormally shaped capillaries surround cysts, while a regression of blood vessels occurs in the remaining renal parenchyma [91, 92]. Cystic tissue is hypoxic, which could contribute to the increased pericystic vascularization by upregulation of HIF1-α/HIF2-α and their targets, which include VEGF. Both HIF1-α and VEGF are elevated in mouse models of ADPKD [93–95]. Furthermore, one study found that serum levels of angiogenic growth factors such as VEGF correlated with the severity of both renal and cardiac changes in young patients with ADPKD [96]. Interestingly, polycystin-1 itself is expressed on endothelial cells, and *Pkd1*-null mice die as embryos because of defects in the integrity of blood and lymphatic vessels associated with inadequate vascular branching, loss of directional migration, and a leakiness that causes profound oedema [97–100]. These findings suggest that vascular lesions in ADPKD are of primary rather than secondary relevance to the disease. The link between high levels of VEGF and

aggressive ADPKD has led to assessment of the value of inhibiting VEGF or its receptor VEGFR in mice, with one study finding a beneficial effect, and another finding the opposite [94, 101]. A study evaluating inhibition of HIF1-α in PKD rodent models did not show any therapeutic effect, but as the agent used, 2-methoxyestradiol, has broad target specificity, the specific importance of HIF1-α to ADPKD is unclear [95].

Deregulating cellular energetics

The “Warburg effect” [102], associated with upregulation of the glucose transporter GLUT1, activation of RAS, overexpression of MYC, and inactivation of p53, describes the high rate of aerobic glycolysis observed in tumours, and has been considered a unique feature of cancer. Hence, it was of extreme interest to the field of ADPKD when a similar high rate of aerobic glycolysis and glucose dependence was identified in ADPKD kidney tissue and relevant mouse models [56, 103, 104]. Mechanistic analyses indicated that the defect represented inhibition of LKB1/AMPK signalling, coupled with strongly elevated levels of mTORC1. Importantly, treatment of two mouse models of ADPKD with the non-metabolizable glucose analogue 2-deoxyglucose limited cyst formation [56]. The finding of altered glucose metabolism in ADPKD has implications for interpreting the biological activity of mTOR inhibitors in patients with this disease [11, 12], as mTOR signals through HIF to induce glucose transporters and glycyolytic enzymes. Glucose is taken into the cell by multiple receptors; interestingly, one study has shown that targeting the sodium-glucose cotransporter (SGLT2) with phlorizin inhibits PKD while inducing glycosuria in a rodent model [105]. In general, very little literature addresses the issue of potential changes in the activity of glucose transporters such as GLUT1 in the context of ADPKD, despite their major roles in cancer, autophagy, and cell energetics.

The discovery of a Warburg (like) effect in ADPKD raises the interesting possibility that additional metabolic changes associated with cancer might also characterize cystic tissues. Of particular note, a subset of tumours do not become glucose-dependent, but instead become ‘addicted’ to glutamine as an energy source, as reflected by a negative reaction to (18)F-FDG PET imaging in vivo [106, 107]. This process involves the upregulation of glutaminase as a downstream consequence of MYC or RAS activity, or as a consequence of loss of VHL and activation of HIF [108, 109]: all of these pathways are relevant to ADPKD pathogenesis. To date, however, the issue of elevated glutaminase activity and potential glutamine dependency remain essentially uninvestigated in ADPKD. As glutamine-dependency suggests potential strategies for therapeutic treatment [108], research in this area would be extremely timely.

Inflammation and immune attack

The seventh and eight hallmarks of cancer are the ability of tumours to avoid immune destruction and promote inflammation. Tumour immunology is a well-developed field [110]. Studies focus both on the mechanisms by which tumours deflect the lethal action of cytolytic T cells and natural killer cells, while attracting macrophage subtypes, mast cells, neutrophils, and lymphocyte subtypes to promote an inflammatory environment conducive to tumour growth. To date, little, if any research, has assessed the potential role of immune cells in regulating ADPKD development. However, several provocative studies suggest a

positive contribution of infiltrating macrophages to the disease course. One study from 1984 indicated that a germ-free environment limits the onset and progression of renal and hepatic cystic disease in mice that develop cystic kidneys [111]. Interstitial inflammation, characteristic of ADPKD, results in elevated levels of cytokines in the cyst fluid of patients with ADPKD and is thought to contribute to disease progression [112–114]. Indeed, several studies from the past few years have provided evidence that M2-like macrophages can promote cyst growth in ADPKD and in autosomal-recessive PKD (ARPKD), by driving proliferation and fibrosis in the cystic epithelium via a signalling pathway that involves induction of the complement component C3 [115–117]. Interestingly, C3 and other proteins associated with the immune system are highly induced in the kidney following acute kidney injury, a known accelerant for cystogenesis [118]. In a 2014 review, Harris and Torres describe how macrophages might support PKD progression and suggest that activated macrophages could be potential treatment targets [18].

Genomic instability and mutation

Cancer is inherently associated with a progressive acquisition of mutations, often caused by inactivation of p53 or other components of genome surveillance systems. Tumours often comprise polyclonal populations of cells that contain complex patterns of mutations in individual genes, copy number variations including chromosomal gains and losses, and gene-fusion events. Beyond events involving DNA, failures of checkpoint controls allow centrosomal amplification, contributing to mitotic spindle defects that can further destabilize cells.

Although this level of genomic disorganization is not thought to occur in ADPKD, increasing evidence indicates that less dramatic but still important changes affect genome integrity in this disease. A growing body of data suggests that development of renal cysts might initiate from selected clonal populations that have experienced loss-of-heterozygosity (LOH) around the *Pkd1* or *Pkd2* locus [119–121]. This hypothesis is compatible with a classic cancer ‘two-hit’ model [122], although it is also possible that allelic haploinsufficiency, augmented by epigenetic inactivation of *PKD1* [123], could be causative. Using conditional *Pkd1*-knockout mice, Battini and colleagues showed that depletion of *Pkd1* led to rapid and substantial centrosome amplification, multipolar spindles, and evidence of genomic instability and mitotic catastrophe in kidney cells; although the genomes subsequently stabilized, micronucleation, chromatin bridges and aneuploidy remained. Importantly, centrosomal amplification was also observed at both early and late time points during disease progression in mice *in vivo* and in human patients with ADPKD [124]. Another group found that mutated polycystins lead to chromosome segregation and cytokinetic defects and polyploidy [125, 126]. One provocative study found that peripheral blood lymphocytes of patients with ADPKD show higher intrinsic rates of DNA damage, and an increased susceptibility to DNA damage [127]. Both polycystin 1 and polycystin 2 are functionally expressed in B-lymphoblastoid cells [128, 129], while polycystin 1 is also expressed in peripheral blood lymphocytes [130]. Interestingly, three studies of renal ciliopathies have shown that the initiating mutations involve genes linked to control of DNA damage response signalling, although whether this function or alternative functions of the genes in question are essential for cyst formation is not yet clear [131–133].

Activating invasion and metastasis

Cancer mortality often results from uncontrolled metastasis, a multi-step process that involves many different cellular and molecular mechanisms. These steps include tumour-intrinsic changes, which frequently involve epithelial-to-mesenchymal transition (EMT), involving changes in cell differentiation and polarization; local invasion and intravasation into a nearby vessel; extravasation and colonization in a distant tissue as a micrometastasis; and finally growth into a macroscopic tumour [21].

In one of the most unambiguous differences with cancer, ADPKD cells neither invade nor metastasize. However, beyond this clearly demarcated difference in end point, intriguing similarities exist in sub-processes associated with invasion. First, an early defect that occurs as cancer cells undergo EMT is a change in epithelial apical–basal polarization, associated with altered planes of mitotic spindle orientation. Altered PCP signalling is important in cancer progression, is associated with clinical outcome and can be a driver of cancer metastasis [134–136]. PCP signalling involves tuning of the canonical Wnt pathway (involving signalling through the Frizzled (Fzd) receptor to activate Disheveled (Dvl) and hence inhibit the APC/GSK3β/CK1 destruction complex and increase cytoplasmic β-catenin), and the non-canonical Wnt pathway (in which interaction of inversin/NPHP2 with Wnt/Fzd/Dvl transmits signals to RhoA and Rac to reorganize the actin cytoskeleton). Normal PCP signalling, coordinated at the cell cilium [137, 138], is essential for renal morphogenesis, and both ciliary defects and a number of proteins that are intermediaries in PCP signalling have been associated with cystic kidney disorders [139–142]. Polycystin 1 has been specifically linked to the control of PCP signalling [143–145].

Spindle misorientation has an important role in disrupting the organization of epithelial sheets and supporting cancer progression [146]. In PKD, disorientation of mitotic spindles has been identified as a driver of cystogenesis, particularly in cystic syndromes associated with ciliopathies [140, 141, 147, 148]. However, the connection is not invariant ([149]), and in mouse models of ADPKD, loss of oriented cell division is not thought to be responsible for cyst initiation, but rather thought to develop when tubules are already dilated [150]. In contrast, loss of oriented cell division in a mouse model of ARPKD was not associated with cyst development [150].

As noted above, a prominent feature of ADPKD is fibrosis [41], associated with upregulation of TGF-β, which classically induces EMT in transformed cells [151]. E-cadherin, which anchors adherens junctions and supports cell polarity, is typically downregulated in cancer. In ADPKD, E-cadherin, along with other proteins that regulate cell polarity, is trapped cytoplasmically, potentially due to a failure of recruitment by polycystin-1 [152, 153]. EMT-associated proteins including smooth muscle actin and Snail are downregulated in cystic tissue [154, 155], as in cancer cells that have undergone EMT. Typically, cancer cells that have become mesenchymal are more migratory. Some evidence suggests that the polycystin 1 and proteins associated with its function regulate cell migration in cancer [156] and in normal development [98]; how these processes are affected in the context of ADPKD requires further study. Proteins involved in interaction with the ECM and interpretation of ECM signals for growth, including integrins, the prometastatic protein Nedd9, and their effector, Src, are upregulated with cystogenesis, and some

preclinical studies targeting these proteins suggests efficacy in reducing cyst growth [43, 44, 157, 158].

ADPKD beyond the hallmarks of cancer

The preceding discussion described many commonalities between ADPKD and features commonly associated with cancer. However, at least two key features of ADPKD are not typically considered traits of cancer: altered ciliary signalling and changes in intracellular levels of calcium and cAMP, which promote cell proliferation and polarized fluid secretion (Figure 1).

Altered ciliary signaling

A major breakthrough in the study of ADPKD was the recognition that polycystins 1 and 2 localize, heterodimerize, and signal at the cilium [18, 159, 160]—a small organelle that is frequently described as an ‘antenna’, and protrudes into the extracellular space to receive mechanical and molecular signals from the environment. In the kidney, the single, non-motile primary cilium protrudes into the lumen of renal tubules and transduces cues from renal flow and small molecule ligands to regulate intracellular signalling. In addition to polycystin signalling, the cilium is a hub of other signals relevant to ADPKD (and cancer), with cilia expressing receptors relevant to Wnt and PCP signalling, Hedgehog, and other pathways that regulate cell polarity, proliferation and morphogenesis [161].

For more than a decade, much of the thinking about cystic disorders centered on the observation that mutational loss of proteins required for cilia formation often led cystogenesis [162–164]. In this view, the primary function of ciliary signalling was to restrain cyst formation. However, an important 2013 study by Ma *et al.* found that genetically induced loss of cilia in mice ameliorated cystogenesis induced by defects in either *Pkd1* or *Pkd2* [165]. This finding was corroborated by another study, in which administration of a drug that stabilized cilia by inhibiting the cilia disassembly-promoting kinase Aurora-A exacerbated cystogenesis caused by a mutant *Pkd1* [157]. These findings suggest that significant differences might exist in the aetiology and signaling dependency of cysts originating from loss of cilia and those induced by mutation of the polycystins. In ADPKD—caused by polycystin mutations—maintenance of the cilium to enable defective cyst-promoting signalling is important for disease pathogenesis. By contrast, mutations affecting proteins such as IFT27 and IFT88, which are associated with ciliopathies that arise from the absence of cilia, might accelerate the cell cycle through the removal of checkpoints (see below for further discussion).

This distinction is important when comparing the role of cilia in ADPKD and in cancer, a disease in which ciliary dysfunction might also be considered typical. For the majority of cancer types, including RCC, transformation and cancer progression includes downregulation of cilia [166–171]. Debate is ongoing as to whether loss of cilia in cancer is causative or correlative [172]. In some cases, the presence or absence of cilia has consequences for the therapeutic response; for example, in medulloblastoma and cholangiocarcinoma [173, 174]. The role of ciliary integrity and signalling requires further study in cancer, particularly given the evidence that retention of cilia might serve as a

checkpoint for cell cycle reentry [175, 176]—a topic highly relevant to tumour cell quiescence. The oncogene Aurora-A is elevated in many cancers. While its primary oncogenic function is often attributed to the role of hyperactive Aurora-A in inducing genomic instability [177], Aurora-A may also contribute to cell transformation by inducing ciliary disassembly [167, 178]. In addition to its other functions noted above, the VHL tumor suppressor also has a role in regulating cilia. VHL is the substrate recognition component of a E3 ubiquitin ligase complex that includes Cul2, Rbx1, elongin B and elongin C [179]. This complex targets HIF for degradation and its actions are normally oxygen-dependent [180]. Loss of VHL results in HIF accumulation and downstream transcription of various targets including VEGF and NEDD9 [181–184], which results in activation of NEDD9-dependent Aurora-A and destabilization of primary cilia [185]. Hypothetically, the requirement for cilia retention in ADPKD versus cilia loss in RCC might be an important discriminating factor of the two diseases.

Calcium, cAMP and polarized fluid transport

One defining feature of ADPKD is the accumulation of fluid in cysts. A topic of study for over 30 years [186], the mechanisms underlying fluid secretion in ADPKD are now both well-defined and primary targets of inhibition in ongoing preclinical and clinical studies [187, 188]. The elevated transepithelial fluid secretion into nascent cysts in ADPKD leads to cyst growth and expansion, compressing and subsequently destroying the neighbouring renal parenchyma and causing a decline in renal function. This fluid secretion is mainly driven by transepithelial Cl^- secretion, with Cl^- entering the epithelial cell through the basolateral Na/K/2Cl cotransporter NKCC1, and exiting into the lumen through the cAMP-activated apical Cl^- channel CFTR, with additional ion channels and pumps (for example, KCa3.1 and Na^+/K^+–ATPase) providing ion homeostasis. As a result, water follows an osmotic gradient, with basolateral intake and apical secretion mediated through aquaporins; apical–basolateral separation is maintained through action of non-leaky tight junctions, contributing to fluid accumulation in the cysts. cAMP is the major driver of this process, with cAMP levels elevated in precystic kidneys [189]. Mechanistically, depression of intracellular Ca^{2+} in the context of mutated *PKD1* or *PKD2* reduces the repression of basolaterally localized adenylyl cyclase (AC). This effect, coupled with arginine vasopressin (AVP)-mediated stimulation of AC, strongly elevates AC-mediated production of cAMP, which drives CFTR [187, 188, 190].

The imbalance of Ca^{2+} and cAMP levels is important for ADPKD pathogenesis in another way: the control of cell proliferation. Following depression of Ca^{2+} levels, kidney cells switch from a cAMP-inhibited to a cAMP-dependent proliferative. This switch is associated with upregulation of B-RAF and ERK, due in part to removal of inhibition of B-RAF by AKT, a kinase dependent on sufficient Ca^{2+} levels [83, 190]. Further, the cAMP-dependent phenotype of ADPKD kidney epithelial cells can be reversed by elevating intracellular Ca^{2+} levels, for example, by administration of Ca^{2+} ionophores or Ca^{2+} channel activators [191]. By contrast, although remodelling of Ca^{2+}-dependent signalling is strongly associated with cellular transformation, many oncogenes depend on localized elevations in Ca^{2+} to support their function [192]. The role of cAMP in cancer is not uniformly growth-promoting as in ADPKD; rather, in some cancer cells it is growth-promoting and in others growth-inhibiting,

with compartmentalized signalling in cellular microdomains having an important role in this distinction [193].

Therapeutic strategies that have targeted regulators of cAMP and ion transporters have been tested successfully in preclinical and clinical studies of ADPKD, emphasizing the relevance of these transport and cell proliferation properties to the disease [187]. The vasopressin V2-receptor antagonist tolvaptan has shown some success in clinical trials of ADPKD [194, 195]; however, adverse effects, including a decreased ability to concentrate urine, and hepatic toxicity [196] pose challenges to its use by patients. Somatostatin analogues, which inactivate AC, are also under investigation in clinical trials; additional targets being assessed in preclinical studies include the basolateral KCa3.1, regulators of intracellular Ca^{2+} and cAMP levels, as well as molecules involved in the regulation of CFTR, NKCC1 and the aquaporins [187].

Some studies indicate a role for ion and water transport regulation in tumour pathology. For instance, inhibition of KCa3.1 or the Na/K/2Cl cotransporter and subsequent changes in fluid movements can inhibit tumour cell invasion in brain tumours [197–201]. Similarly, aquaporins drive cell migration and invasion and are strongly expressed, particularly in aggressive tumours of various types [202]. Other studies indicate a role for CFTR as a tumour suppressor [203], whereas vasopressin has been described as an autocrine growth factor for non-small-cell lung cancer [204]. Surprisingly, very few investigations have been made into the role of these important signalling systems in RCC; this area seems worthy of more attention.

Cancer in ADPKD; cysts in RCC

The fact that signalling and process changes associated with ADPKD are similar to those involved in cancer raises the interesting possibility that patients with mutations in *PKD1* or *PKD2* might be predisposed to kidney cancer, given that they are already ‘part way there’ in terms of the number of cancer hallmarks they possess. Some studies suggest that an intracystic papillary ‘tuft-like’ proliferation seen in patients with ADPKD might be a precursor to RCC [205–207]; however, no definitive evidence exists to support such an association. This lack of evidence is in large part due to limitations in the design or power of studies that have addressed this question [208–211]; for example, one retrospective study examined nephrectomized kidneys from 79 patients with ADPKD, and found that the prevalence of RCC in patients with ADPKD and ESRD who had been on dialysis for more than 1 year or had undergone renal transplantation was 2–3-fold higher than that of patients with ESRD alone. However, a major limitation of that study was that the patients with ESRD were from a completely different study [211]. Another group of researchers investigated the prevalence and incidence of cancer in 823 patients with ADPKD and ESRD over 16 years of follow up. From the first to the second 8-year interval of observation, the prevalence of cancer increased by 35% ($P = 0.0002$) while the incidence of cancer remained stable. This apparent disparity could be explained by an increasing age at onset of ESRD for patients with ADPKD. This study did not compare these data to patients without ADPKD, however, and the prevalence of RCC in ADPKD patients with ESRD was <1%, limiting the ability to draw conclusions from this study [208].

The most rigorous study to date used data from the Scientific Registry of Transplant Recipients to analyze the incidence of new cancers among 10,166 kidney transplant recipients with ADPKD versus 107,339 transplant recipients without ADPKD. After multivariable adjustment (particularly for age), risk of kidney cancer waslower in transplant recipients with ADPKD than in those without (adjusted incidence rate ratio (IRR) 0.70, 95% CI 0.51−0.93, $P = 0.013$) [212]. A particularly unexpected finding was that the rate of non-kidney cancer was also lower in patients with ADPKD than in those without (adjusted IRR 0.83–0.84, $P < 0.0001$). Similarly, a 2011 study suggested that a loss-of-function mutation in the ARPKD-associated gene *PKHD1* (which encodes fibrocystin) provides protection against colorectal cancer [213], whereas a 2014 study indicated that overexpression of intact polycystin 1 or polycystin 2 promotes colorectal cancer aggressiveness [214].

Approaching the issue a different way, one can ask whether RCC is associated with prior or parallel formation of kidney cysts. RCC defines a histologically, genetically and molecularly heterogeneous group of tumours of the kidney that arise from the epithelial lining of renal tubules [215]. Although the WHO sub-classified RCC into ten malignant and four benign types in 2004, more variants have since been identified. In 2013 the International Society of Urological Pathology (ISUP) Vancouver Consensus Statement added five more malignant epithelial tumour subtypes and three provisional subtypes [216]. By age 50, up to 50% of the population has at least one simple renal cyst, which is typically considered benign [217]. However, the formation of cysts is a shared feature of a number of RCC variants, including the two that together comprise ~90% of RCCs—clear cell RCC and papillary RCC—and in particular is a feature of the eponymous cystic RCC (comprising 5–7% of all malignant RCCs) [210, 218, 219].

Whether cysts are more generally precursors to RCC is controversial. Certainly, most cases of clear cell RCC are not associated with known prior cysts. Conversely, some cysts certainly can become malignant. The Bosniak classification has become a worldwide standard in categorizing cystic lesions using imaging, to predict likelihood of developing malignancy [220, 221]. Under the Bosniak system, cysts vary from category I simple cysts that have no appreciable malignant potential, to category III and IV complex cysts that are often or almost uniformly malignant, respectively, leaving those in category II and IIF as a common clinical dilemma [222]. The extent to which signalling in these cysts reflects the signalling pathways of cysts in ADPKD is largely unexplored, although some studies of ADPKD, such as the study by Ma *et al.* described above, which found that loss of cilia ameliorates cystogenesis in a mouse model of ADPKD, [165], demonstrate that the nature of the cystogenesis stimulus can profoundly affect the underlying biology of the cyst. Intriguingly, close inspection of The Cancer Genome Atlas (TCGA) [223] indicates that damaging mutations in *PKD1* and PKD2 are found in a subset of tumours for a number of cancer types. Whether such mutations interact with normal cancer-promoting oncogenes to have an effect on tumour pathogenesis is currently unknown.

In considering the underlying genetics of ADPKD and RCCs, we know that ADPKD cysts arise from focal LOH leading to hemizygous expression of the damaging *PKD1* or *PKD2* alleles, although even heterozygous expression of mutant alleles can affect cell proliferation [224]. Notably, the most common oncogenic drivers and tumour suppressors for other types

of cancer are not the primary drivers for RCC. In sporadic clear cell RCC, which is by far the most common RCC subtype (comprising ~80% of all RCCs), inactivation of the tumour suppressor *VHL* is almost a *sine qua non*, whereas other RCC subtypes, including papillary, chromophobe and oncocytic, do not generally depend on the VHL pathway [225]. The *VHL* gene, originally discovered in 1993 as a precursor germline mutation in von Hippel–Lindau (VHL) disease, is located on chromosome 3p25, and biallelic *VHL* inactivation is noted in over 90% of sporadic clear cell RCCs [226]. *VHL* inactivation can occur via a mutation (evident in ~50–80% of tumours), but also by hypermethylation and LOH, with less than 5% of clear cell RCCs exhibiting no VHL involvement [227, 228].

Patients with VHL disease (involving germline transmission of a damaged *VHL* allele) are at a very high risk of developing clear cell RCC, with an incidence rate of up to 70% compared with a 1.6% lifetime cumulative risk of kidney and renal pelvis cancer in the general population [229]. Patients with VHL disease are also at increased risk of developing cystic lesions [230], paralleling the cystic disease seen with loss of VHL in mice, discussed above. Two studies of patients with VHL disease showed that morphologically normal epithelial cells lining renal cysts, as well as early dysplastic lesions, showed loss of the remaining *VHL* allele, a finding that was considered to be compatible with the idea that cysts are potential precursor lesions for clear cell RCC. However, VHL disease might be considered an exception rather than a specialized case [231, 232].

In human RCC, genomic characterization and directed studies have indicated that loss of *VHL* is accompanied by a recurrent mutation that activates the PI3K pathway and mutation of genes involved in chromatin remodelling (*PBRM1, ARID1A* and *SMARCA4* in the SWI/SNF complex), and reprogramming of cellular metabolism, including controls of glycolysis [164, 233, 234]. These integrated changes are probably necessary for progression to RCC. Recent work arising from The Cancer Genome Atlas [233] as well as other large sequencing studies [235] has further elucidated the molecular genetics of clear cell RCC. Common targets of mutations include a number of other two-hit tumor suppressor histone modifying and chromatin remodelling genes, including polybromo 1 (*PBRM1*) (mutated in ~45% of clear cell RCC) [236], *BAP1* (mutated in ~10–15% of clear cell RCC, and associated with aggressive disease) [237], and SET domain containing protein 2 (*SETD2*, mutated in 10–15% of clear cell RCC) [238]. All three genes are located on chromosome 3p, as is *VHL* and as noted earlier, inactivation of both *VHL* and *Bap1* in mice leads to both cystic and neoplastic lesions [86]; clearly, definition of the functional interactions between *VHL, BAP1, PBRM1*, and *SET* is a topic of urgent interest. Other common, but less frequently mutated genes in sporadic clear cell RCC include *PTEN, MTOR, PIK3CA, TCEB1, KDM5C, TSC1* and *JARID1c*; provocatively, some of these are also affected in PKD [233, 235, 239].

The cyst versus cancer bifurcation

Given the strong evidence that a cystic condition can readily progress to cancer in the context of *VHL* mutations, it seems even more remarkable that ADPKD predisposes against, rather than towards, RCC. In reviewing the degree to which ADPKD aligns with cancer hallmarks, many convergences are evident. Points of difference that stand out in ADPKD

include a tendency to apoptosis rather than autophagy, decreased intracellular calcium levels, and a strongly polarized phenotype, including retention of cilia and polarized fluid secretion. These phenotypes are associated with the cells' restriction to a monolayer and a failure to invade through basement membranes. On the basis of these differences, some speculation about the origin of the diseases and potential implications for their treatment are possible.

Founder mutations bias subsequent mutations

Current models for early cancer development describe the gradual proliferative expansion of close-to-normal cells, as mutations that promote a malignant phenotype increasingly become selected within the population. In many cases, early stage transformed cells remain morphologically normal, but because of a higher proliferation rate, they gradually out-compete non-transformed cells, providing a large pool of precursors poised to become highly malignant following a small number of additional mutations. This phenomenon, termed 'field cancerization', is linked to environmental exposure to mutagens in some but not all tumour types [240–242], and underlies the higher risk of recurrence in some types of epithelial tumours following surgical resection of a primary lesion [243].

An initiating lesion in *PKD1* or *PKD2* provides a modest proliferative advantage, activating RAS and inhibiting the APC destruction complex, thereby removing constraints on cell division and contact inhibition. In colorectal cancer, early DNA lesions result in removal of APC and RAS activation [244]. We speculate that by indirectly simulating these DNA lesions, albeit at a lower level, signalling changes associated with ADPKD- could reduce the chances of cancer-associated mutations in the population, by reducing their selective advantage. This model might predict a different pattern **of** mutations in cancers arising with and without ADPKD-associated mutations. This hypothesis could readily be tested.

Barrier function in cystic epithelia and EMT

Both for normal kidney function and development of cysts, the distal tubular epithelia and collecting ducts of the kidney require a non-permeable barrier between cells [245]. This requirement is shared by a limited number of other epithelial linings, such as those surrounding the bile duct—which interestingly is another tissue that is prone to cystic development in ADPKD [246]. These barrier roles are provided by tight junctions (TJs). Major components of TJs are the claudins, of which 24 family members exist in humans, and the occludins, which are multipass transmembrane proteins that stitch together adjacent cells to anchor intracellular components such as ZO-1. Although the large number of claudins makes dissection of their functions difficult, patterns of claudin expression have been shown to change in cystogenesis, and at least one, claudin-7 (CLDN7), is abundantly expressed in cystic linings [247], and prevents Cl^- ion backleak.

In contrast to other classes of cell–cell contact, including most notably the adherens junction, the tight junction has been much less studied in cancer. Nevertheless, changes in TJ proteins, including downregulation of CLDN7 and CLDN8, have been associated with invasion, metastasis, and regional recurrence for some cancer types [248–252]. One intriguing study that investigated the development of colorectal cancer found that inflammatory signalling induced the mislocalization of claudins 3, 4, 5, and 7 and associated

defects in TJ functionality, which supported tumour progression [253]. In breast cancer, a claudin-low phenotype has been strongly associated with EMT and also with tumour initiating cells (sometimes referred to as cancer stem cells) [249], and evidence exists of similar findings in bladder cancer [254]. One provocative speculation that arises from these observations is that the polarized fluid secretion and maintenance of fluid-filled cysts in the presence of increasing hydrostatic pressure associated with cystogenesis, depends on the enforced expression of TJ proteins, thereby imposing a strong block to the downregulation of these proteins that would be required for invasion. In this context, it is intriguing that loss of VHL strongly downregulates E-cadherin, occludin, and claudin 1 in a cell culture model of RCC, causing both TJ assembly defects and facilitating EMT [255]. Further exploration of TJ control as a distinguishing factor between cancer and cysts would be of interest.

Evaluation of anti-cancer agents for ADPKD

What are the consequences of the similarities between ADPKD and cancer signalling pathways for therapy? As is clear from the above comparison, the broad similarities between ADPKD and cancer cells suggest that many agents that slow the proliferation of tumours would have similar effects in limiting the proliferation of ADPKD cells. However, important caveats are that ADPKD is much less lethal than many forms of cancer, and that many cancer treatments have toxic adverse effects that would limit their application in a chronic setting. Hence, for sustained use, only targeted cancer agents with excellent safety and tolerability profiles should be considered for ADPKD. Some early evidence showing that inflammation and macrophage infiltration contribute to ADPKD pathogenesis could suggest that anti-inflammatory agents that target macrophages or elements of the inflammasome [256, 257] might be a well-tolerated strategy to slow cystic growth over the long term. In this context, however, it will be important to select agents that are not nephrotoxic, given the already impaired renal function of patients with ADPKD.

More speculatively, some cancer therapies focus specifically on the phenomenon of oncogene addiction [258]. In this scenario, unique properties of the cancer cell that are associated with expression of a driver oncogene cause those cells to die if the protein is only briefly removed [259]. One emerging example of success with this strategy is with the oncogene c-MYC: tumours with MYC amplification are highly dependent on active transcription, and undergo substantial apoptosis if the transcriptional apparatus is blocked by a cytotoxic agent or targeted agents that inhibit chromatin-remodelling proteins such as BET bromodomain proteins [260]. As noted above, elevated MYC expression is a hallmark of ADPKD cysts; if this elevation, or MYC dependency is specific to cysts (that is, tissue in which the *PKD1* or *PKD2* mutation is hemizygous), brief courses of treatment with an appropriate transcriptional inhibitor would selectively eliminate cyst-forming cells, while leaving normal parenchyma intact. However, great care is needed with this approach, given the extra-renal manifestations of ADPKD; it is possible that dependency on MYC in hemizygous clones for ADPKD mutations in the vasculature might lead to serious consequences. Further, one study has found that high MYC expression is anti-metastatic in breast cancer, inhibiting cell migration and invasiveness [261]. As another caveat, if high MYC actually prevents metastasis in ADPKD patients, then anti-MYC therapy could conceivably promote metastasis (although based on the discussion above, it is likely that a

number of discrete signalling differences contribute to the non-invasive, non-metastatic behaviour of ADPKD cells). As with any therapeutic targeting strategy, preclinical tests will need to be thorough to avoid adverse consequences.

MYC is just one example; directed scrutiny of the signalling changes in ADPKD might suggest other forms of ‘addiction’. For example, genome-wide methylation profiling of ADPKD has identified epigenetically regulated genes that are associated with renal cyst development, including hypermethylation in particular (associated with gene silencing), which affects genes that regulate ion transport, calcium signalling, and cell adhesion, chromatin remodelling, the Wnt/Notch pathway, and *PKD1* itself [123]. Efficacy of histone modifying enzymes in treatment of ADPKD has already been demonstrated ([48]); this research direction has considerable promise.

Overall, the many commonalities between ADPKD and RCC, both in regard to process derangements (Figure 1) and some clinical aspects (Table 1), makes it plausible that treatment strategies developed for one disease might be applicable to the other. For example, AMPK activity is reduced in both ADPKD and RCC [262, 263], and activation of AMPK by metformin can yield therapeutic benefit in both diseases. AMPK activity can also be increased through its upstream activator LKB1; LKB1 activity is enhanced by phosphorylation downstream of receptor tyrosine kinases such as MET, and hence might be indirectly affected by MET inhibition by cabozantinib and foretinib, drugs that have been evaluated in RCC [264, 265] (Figure 2).

Cancer prevalence and implications for ADPKD

As mentioned earlier ADPKD affects approximately 1 in 500 individuals whereas 35–40% of individuals will develop some form of cancer in their lifetime, and one in four individuals will die of their cancer [266]. Hence, while very few patients with cancer will need to deal with ADPKD, even with the potential protective effects of a *PKD1* or *PKD2* mutation, a very large percentage of patients with ADPKD will receive anticancer therapies. Many of these therapies will include cytotoxic drugs; increasingly, these therapies include the use of targeted agents. Based on the discussion above, which shows both increased genomic instability and altered signalling in the context of ADPKD mutations, it is very plausible that these underlying features will affect the activity of cytotoxic and targeted drugs in both the tumour and in normal tissue. The effects of the ADPKD genotype might result in a better or worse response to therapy, and a better or worse cytotoxicity profile with specific clinical agents. To our knowledge, no clinical trial or retrospective analysis has assessed these possibilities; indeed, such a trial would be difficult to run, given the diverse forms of cancer and many treatments available, and the (relatively) limited size of the ADPKD patient population. At this time, a number of mouse models for ADPKD are available, and it is relatively easy to establish overexpression and knockout models for *PKD1* and *PKD2* in human cancer cell lines for genes of interest. Use of such tools to explore the specific consequences of common lesions associated with ADPKD and their response to the agents most commonly used for cancers might yield extremely valuable insights that help provide ‘precision’ or personalized medical outcomes for patients with cancer who are also afflicted with ADPKD

Finally, as with most diseases with onset in mid or late life, many patients with either ADPKD or cancer will experience comorbidities, which can significantly impact disease progression and survival [267]. As one important example, ADPKD is associated with a high prevalence of hypertension, in part because of defects in the renin–angiotensin–aldosterone system (RAAS) that are fundamentally related to the aetiology of the disease. Control of blood pressure with agents such as the angiotensin-converting-enzyme (ACE) inhibitor lisinopril has shown promise in clinical trials of ADPKD [268–270]. Many cancer treatments, including targeted therapies that inhibit VEGF and other proteins, or chemotherapies, can induce hypertension [271], and many patients with cancer have hypertension even prior to diagnosis. Data from the past 20 years raises the possibility that RAAS defects and hypertension are also independent risk factors for cancer, although the mechanism linking these entities remains to be resolved and the topic is at present controversial [272–274]. In developing integrated therapies for patients with comorbidities, management of orthogonal inputs such as hypertension and obesity might have broad benefits in generally limiting disease progression.

Conclusions

Although PKD has been a topic of scientific study for over a century [275], the degree of investment in the treatment of this disorder has been relatively modest and it has only been in the past two decades that the molecular basis of the disorder has come into focus. By contrast, cancer has been studied for over two millennia, from the time of Hippocrates and Galen, and in the modern age, efforts to understand and control this disease have attracted substantial financial resources. The much greater knowledge base for cancer has supported the early emergence of an overarching conceptual architecture to integrate the multiple cellular defects associated with malignant disease: the cancer hallmarks [21]. As the above discussion indicates, viewing the features of ADPKD in this mirror reveals a surprising number of similarities, enabling a rough alignment of ADPKD with the hallmarks of cancer developed by Hanahan and Weinberg. Key differences between ADPKD and cancer also exist, however, involving (for instance) the obligate maintenance of cell polarity and barrier function. These differences could potentially represent fundamental defining properties of ADPKD compared to cancer, in contrast to properties such as increased proliferation or genomic instability, in which ADPKD possesses similar defects as tumour tissue, but to a lesser degree.

We suggest this comparative analysis could benefit not only the treatment of ADPKD but could also deepen our understanding of cancer biology, by providing an orthogonal source of insight. The majority of anticancer treatments, whether cytotoxic or targeted, are designed to inhibit proliferating tumour cells. However, the substantial majority of cancer deaths arise from uncontrolled metastasis. ADPKD conserves substantial signalling related not only to proliferation and survival as seen in cancer, but also partially conserves the signalling related to tumour invasion. Nevertheless, metastasis is not a feature of ADPKD. Future studies in which members of the cancer community contemplate this mysterious absence of metastasis in the presence of proliferation and survival signals could help focus research on the most lethal features of this disease.

Acknowledgments

We apologize to those of our colleagues whose work we were unable to cite because of reference limits. We are very grateful to Dr. James Calvet and Dr. Jared Grantham (University of Kansas Medical Center), who generously provided many useful suggestions and comments on the manuscript. We also thank the reviewers of this article, for their valuable critiques. The authors were supported by funding from the PKD Foundation and DOD PRMRP W81XWH-12-1-0437/PR110518 (to E.A.G.), from the German Research Foundation SE2280/3-1, Köln Fortune 252/2013 and by the German Ministry of Science and Education (BMBF) as part of the MILES consortium (grant 01ZX1406) (to T.S.-N.), Pfizer independent grant #11703561 (to D.M.G.), BE2212, SFB829, SFB832 (to T.B.); and by NIH Core Grant CA06927 (to Fox Chase Cancer Center).

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Key points

- For over a decade, the ‘hallmarks of cancer’ have provided a unifying framework for the complex set of cell, tissue, and organismal defects associated with malignancy
- Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common inherited disorder with pathological features that echo those found in cancer
- A systematic evaluation of ADPKD in the context of the ten cancer hallmarks emphasizes a surprising degree of similarity in signalling defects associated with the disease
- Two key signalling processes involved in ADPKD—ciliary signalling and control of Ca^{2+}/cAMP and polarized secretion—are not currently thought to be hallmarks of cancer
- The pattern of conserved and distinct signalling pathways emphasizes important issues relevant to the optimal treatment of patients with ADPKD

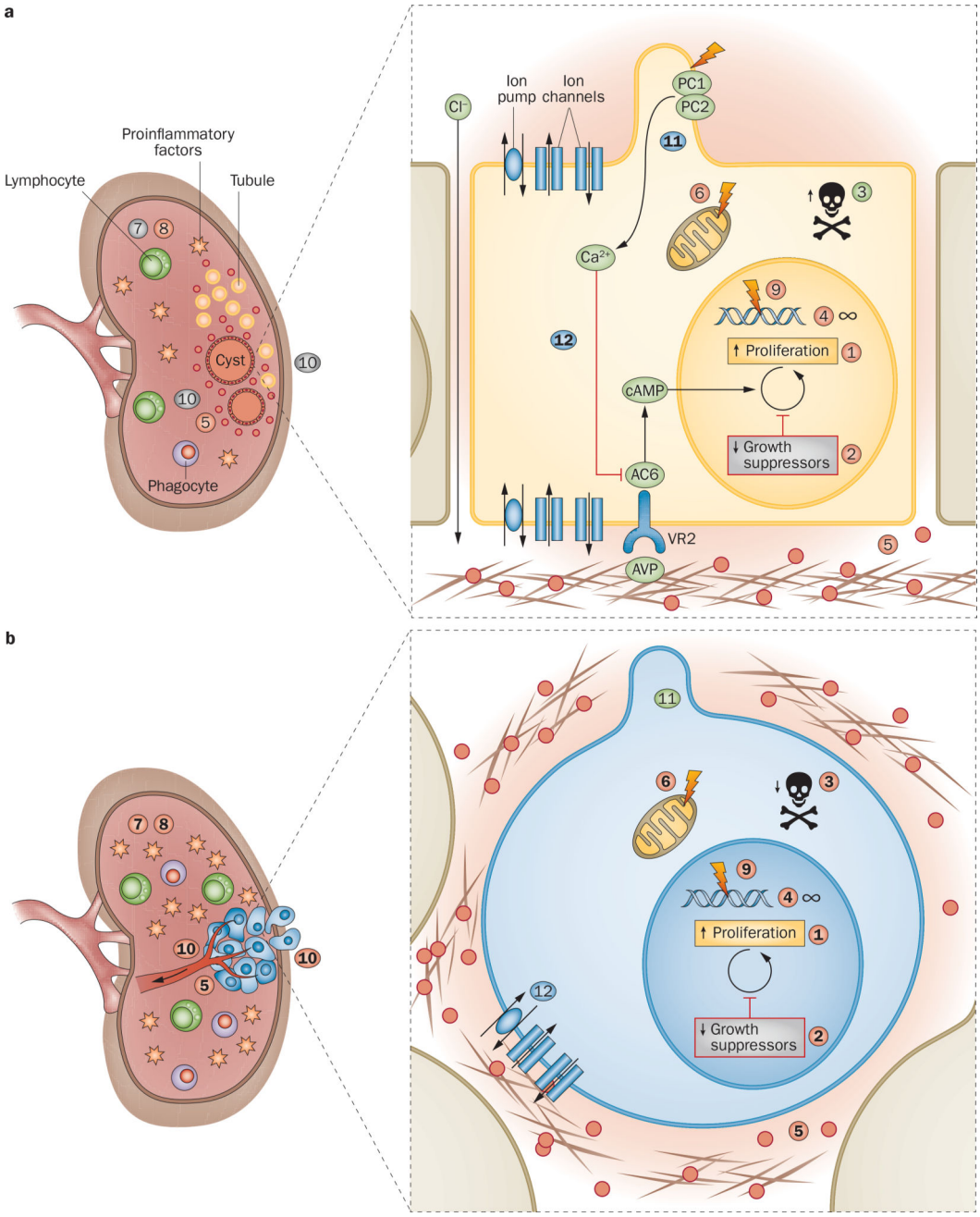

Figure 1. A comparison of the pathological features of autosomal dominant polycystic kidney disease (ADPKD) and kidney cancer

Pathological features and key signalling pathways are indicated for a | ADPKD and b| kidney cancer. Numbers indicate hallmarks originally defined in cancer: (1) sustained proliferative signalling; (2) evasion of growth suppressors; (3) resistance to cell death; (4) replicative immortality; (5) induced angiogenesis; (6) deregulated cellular energetics; (7) avoiding immune destruction; (8) tumour –promoting; (9) genomic instability and mutation; and (10) invasion and metastasis; coupled with features first noted as important for ADPKD, including (11) altered ciliary signalling, and (12) changes involving calcium, cAMP and polarized fluid transport. Hallmarks of cancer are indicated in red where relevant, with bold

numbers reflecting a strong association with the disease; ‘hallmarks’ of ADPKD are indicated in blue. Where a process is affected, but non-equivalently in ADPKD and cancer, it is indicated in green. Where a hallmark is not relevant or has been little studied in a given disease, it is indicated in gray. Abbreviations: AC6, adenyl cyclase type 6; V2R, vasopressin type 2 receptor; PC1/2, heterodimer of polycystins 1 and 2.

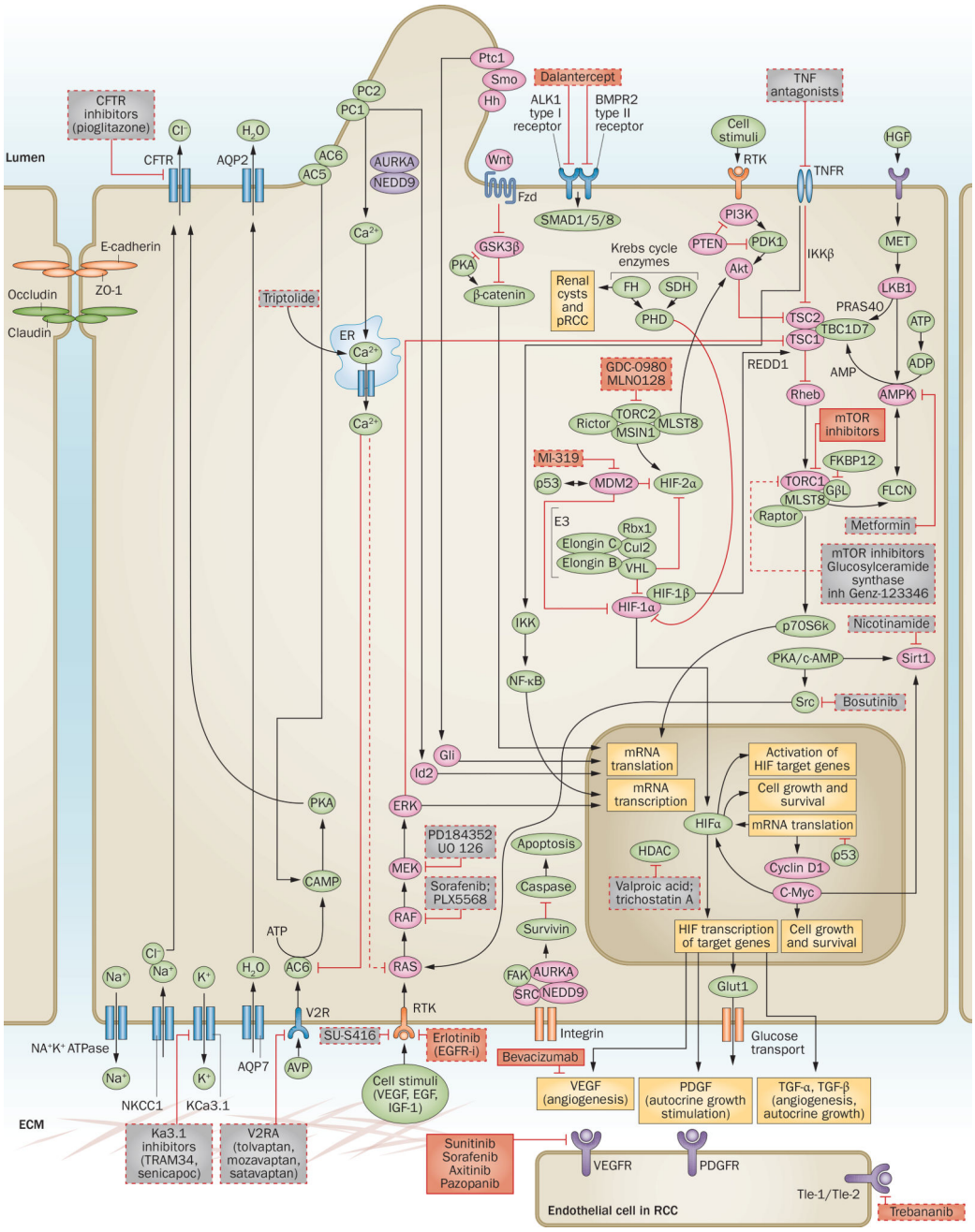

Figure 2. Signalling and drug targets relevant to the pathogenesis of ADPKD and kidney cancer

Pink ovals indicate signalling proteins that are involved in both ADPKD and renal cell carcinoma (RCC). Black arrows indicate positive regulation, whereas red lines indicate negative regulation. Dashed borders around therapeutic agents indicate drugs that are not approved but are being tested; solid borders reflect agents that are FDA-approved for metastatic RCC. Gray boxes indicate drugs that have been tested in ADPKD, whereas red boxes indicate drugs that are used or are being tested in RCC. Drugs listed for RCC include

only FDA-approved agents or select agents that have been clinically tested in humans; drugs for ADPKD include those that have been tested clinically and preclinically.

Table 1

Comparison of the clinical features of ADPKD and RCC.

Features	ADPKD [1, 53, 276–278]	Renal Cell Carcinoma [215, 216, 279–281]
Epidemiology	• Prevalence: 1:400 to 1:1000	• 2% of adult malignancies • Globally ~270,000 cases per year and ~116,000 deaths per year
Risk Factors	• Inherited genetic defects in *PKD1* or *PKD2*	• Cigarette smoking • Obesity • Hypertension • Inherited susceptibility
Pathologic features	• Tubular atrophy • Interstitial fibrosis • Vascular abnormalities • Interstitial infiltrates	• Over 15 pathologic subtypes • Clear cell RCC accounts for ~70–80% of RCC and papillary type I and II for ~10–15% of RCC
Genetic features	• 78% have genetic defect in *PKD1* • 13% have genetic defect in *PKD2* • 2% have genetic defects in PKD1 and *TSC2* • 9% have no mutation detected	• Occurs in sporadic and hereditary (5–8% of RCC) forms • Hereditary syndromes include Von Hippel–Lindau disease (*VHL*), Birt–Hogg–Dube syndrome (*BHD*), hereditary papillary renal cell carcinoma (*MET*), hereditary leiomyomatosis renal cell carcinoma (*FH*), tuberous sclerosis (*TSC1, TSC2*) and succinate dehydrogenase B–associated renal cancer (*SDHB*) • Multiple cytogenetic abnormalities
Clinical presentation	• Fluid-filled cysts: complications include haematuria and urinary tract infection • Enlarged organ: flank and abdominal pain, compression of neighbouring organs • Malfunction: progressive renal failure, concentration defects, nephrolithiasis, hypertension	• Extremely variable with over 50% discovered incidentally • ~30% present with locally advanced or metastatic disease • Classical presentation of advanced disease includes haematuria, flank pain and abdominal pain, but is seen in only 10–15% of patients • Other symptoms of advanced disease may include anaemia, hypercalcaemia, weight loss, fatigue and fevers
Extrarenal manifestations	• Cerebral aneurysms • Hepatic and pancreatic cysts • Cardiac valve disease • Colonic diverticula • Abdominal wall and inguinal hernia	• Paraneoplastic manifestations may be seen in 20–40% of RCC patients • Includes hypercalcaemia, hypertension, polycythaemia, Stauffer's syndrome, fever, weight loss and fatigue, amyloidosis
Treatment options	• Haemodialysis • Renal transplantation • Antihypertensive therapy (ACEIs or ARBs)	• Surgery for localized disease • Radiation for palliation of symptoms • In metastatic disease, non-specific cytokines such as IL-2 and Interferon-α have been largely

Features	ADPKD [1, 53, 276–278]	Renal Cell Carcinoma [215, 216, 279–281]
		replaced by drugs targeting the VEGF and mTOR pathways
prognosis	• Occurrence of renal failure widely variable (median age 58.1 and 79.7 years for *PKD1* and *PKD2* mutations, respectively)	• Widely variable, from ~95% 5-year overall survival in those with localized disease to under 10% survival in those with metastatic RCC

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin-receptor blocker; RCC, renal cell carcinoma; TSC2, Tuberous Sclerosis Complex-2.

Table 2

The hallmarks of cancer: Similarities and differences in ADPKD.

Hallmarks of cancer [21]	Features	Similarities and differences in ADPKD
Sustained proliferative signalling	• Autocrine and paracrine growth stimulation mediated by a pro-proliferative microenvironment • Receptor tyrosine kinase activation • Somatic mutation of downstream pathways with defective negative feedback mechanisms	• Modest elevation of cell proliferation levels in cyst lining epithelium [23, 24] • Stimulated oncogenic signalling including growth factors [32, 33], receptor tyrosine kinases [25, 26] and downstream effectors [10, 27–31], whichdrives cystogenesis • Inhibiting pro-proliferative signalling slows cyst growth • Pro-proliferative stimulus during development or following kidney injury drives cystogenesis • Induction of pro-proliferative and disease promoting microenvironment [41, 43, 45]
Evasion of growth suppressors	Inactivation of tumour suppressor genes including regulators of the cell cycle (e.g. p53, Rb), mediators of ‘contact inhibition’ (e.g. LKB1, NF2) and signalling molecules that limit cell growth (e.g. Hippo/LATS and TSC2)	• Deregulated tumour suppressor signalling (e.g. involving p53, Rb, p21) resulting in either activation or inactivation of growth suppressors [46–51] • Inactivation of growth suppressors associated with cystic kidney disease (e.g. LKB1, Hippo/LATS) [55–58]
Resisting cell death	• Limitation of apoptosis • Deregulated autophagy mediating either tumour cell survival or tumour cell death • Necrotic cell death releasing proinflamatory signals and regulatory factors to promote tumour progression	• Generally low levels of apoptosis found in cyst lining epithelium but elevated compared to normal tubular epithelium [66, 67] • Apoptotic factors are found both to induce or attenuate cystogenesis [68–71] [66, 72] • Suppression of autophagy implicated in ADPKD pathogenesis [56, 73–75] • The necrosis associated proinflammatory cytokine TNF promotes cystogenesis [76]
Enabling replicative immortality	• Overcoming senescence and replicative crisis • Ability to maintain telomeric DNA through upregulation of telomerase	• Replicative crisis delayed in Pkd1−/− MEFs [46] • *VHL* inactivation, associated with renal cancer and renal cysts, can induce senescence or longevity in different model organisms [87–89]
Inducing angiogenesis	• ‘Angiogenic switch’ Upregulation of angiogenic factors by oncogene signalling, hypoxia and immune cells • Pericyte coverage to maintain neovasculature • Migration of ‘vasculature progenitor cells’ derived from bone marrow	• Rich net of abnormally shaped capillaries surrounding cysts while remaining parenchyma shows regression of blood vessels [91, 92] • Hypoxic conditions and upregulation of proangiogenic factors (HIF1-α, VEGF) in cystic tissue with high levels of VEGF being associated with disease aggressiveness [93–96] • In preclinical settings inhibiting angiogenic factors shows either conflicting results (VEGF/VEGFR) [94,

Hallmarks of cancer [21]	Features	Similarities and differences in ADPKD
		101] or no therapeutic effects (HIF1-α) [95]
Deregulating cellular energetics	• Glycolytic switch to an 'aerobic glycolysis' • Increased uptake and utilization of glucose • Oncogenes and hypoxia drive upregulation of glucose transporters and enzymes of the glycolytic pathway • Some tumours have two subpopulations of cancer cells, being symbiotic in their energy metabolism	• High rate of aerobic glycolysis and glucose dependence in ADPKD [56, 103, 104] • Treatment with the non-metabolizable glucose analogue 2-deoxyglucose (2DG) limits cyst formation in rodent ADPKD models [56] • Targeting the sodium–glucose cotransporter (SGLT2) inhibits PKD in a rodent model, while inducing glycosuria [105]
Avoiding immune destruction and tumour-promoting inflammation	• Avoiding immune destruction: tumour cells being less immunogenic, secreting immunosuppressive factors, recruiting immunosuppressive cells • Tumour microenvironment promotes tumour growth through inflammatory immune cells and the secretion of cytokines by fibroblasts, endothelial cells, pericytes and cancer cells	• Interstitial inflammation is characteristic of ADPKD and is speculated to contribute to disease progression [112–114]. • M2-like macrophages can promote ADPKD and ARPKD associated cyst growth via signalling that includes induction of the complement component C3 [18, 115–117].
Genomic instability and mutation	• Progressive acquisition of mutations affecting amongst others the genome surveillance systems (most notably p53) • Failures of checkpoint controls can further destabilize cells	• Indication that loss-of-heterozygosity around the *Pkd1* or *Pkd2* locus initiate cysts [119–121]; alternatively epigenetic inactivation of *PKD1* [123] • Centrosomal amplification in rodent models and ADPKD patients [124] • Mutated polycystins lead to chromosome segregation and cytokinetic defects and polyploidy [125, 126] • Lymphocytes from ADPKD patients show higher rates of DNA damage
Activating invasion and metastasis: dialog with the microenvironment	• Tumour intrinsic changes including EMT/MET, cell differentiation and polarization • Gain and loss of cell-cell/matrix attachment proteins • Crosstalk with cells of the tumor TME • Invasion–metastasis cascade: invasion, intravasation, extravasation, micrometastases, colonization	• No invasion/migration of ADPKD cells • Similarities in sub-processes associated with invasion: disrupted PCP [139–145], mitotic spindle misorientation [140, 141, 147–150], deregulation of EMT markers/drivers (TGF-β, E-cadherin) [41, 152–155] • Polycystin 1 and proteins associated with its function regulate cell migration in cancer [156] and in normal development [98] • Proteins involved in the interaction with the ECM are upregulated (SRC, integrins, NEDD9) and their inhibition impacts cystogenesis in preclinical models [43, 44, 157, 158]

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; ECM, extracellular matrix; EMT, epithelial-to -mesenchymal transition; MEFs, mouse embryo fibroblasts; MET, mesenchymal-to-epithelial transition; PCP, planar cell polarity; PKD, polycystic kidney disease; TME, tumour microenvironment.