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NEPHROLOGY - REVIEW

The association between autosomal dominant polycystic kidney disease and cancer

Ke Sun[1] · Dechao Xu[1] · Changlin Mei[1]

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Abstract
Autosomal dominant polycystic kidney disease (ADPKD) is considered as a tumor-like disease because there are many biological similarities between ADPKD and cancer. However, the commonalities between them are provocative, particularly under the conditions of recent clinical studies. In this paper, we review clinical studies about the association between cancer and ADPKD, and compare the biological characteristics between them, with focusing on cell proliferation, differentiation, migration, apoptosis, and polarity. With detailed literature reviewing, we believe that ADPKD patients have a higher risk of tumorigenesis and thus highly recommend being aware of tumorigenesis during follow-up in patients with ADPKD.

Keywords ADPKD · Cancer · Association

Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited kidney disorder with an incidence of 1/1000–1/400 [1, 2], and it is the result of genetic mutations in *PKD1* (encoding polycystin-1, PC1, accounting for 85% of all cases) or *PKD2* (encoding polycystin-2, PC2, accounting for the remaining 15%) [3, 4]. ADPKD is characterized by the progressive enlargement of bilateral renal cysts, which leads to advanced end-stage renal disease (ESRD) in 50% of ADPKD patients by the age of 60. It is also associated with many extra-renal manifestations, including polycystic liver, pancreatic and biliary dilatation, colonic diverticulosis, cardiac valve abnormalities, and intracranial aneurysms [5–7]. Although the phenotype of ADPKD patients are highly variable, they have some common pathophysiological characteristics: abnormal cell proliferation and apoptosis, abnormal cell polarity and differentiation, increased secretion of epithelial cells, extracellular matrix remodeling, and aberrant interstitial fibrosis [8]. Many of these biological properties are also found in cancer, including enhanced cell proliferation and dedifferentiation, which are thought to be processes that drive the formation of tumors by up-regulating proto-oncogenes [9, 10]. Previous studies also have reported the occurrence of renal cell carcinomas (RCCs) in ADPKD-affected kidneys [11]. Thus, ADPKD has long been considered as a tumor-like disease. In this review, we discuss the relationship between ADPKD and cancer in terms of their biological characteristics and examination in clinical studies, and we highly recommend being aware of tumorigenesis during the follow-up in patients with ADPKD.

Biological characteristics of ADPKD and cancer

Tumor formation and growth are complicated events that involve defects in multiple cellular processes, including cell proliferation, differentiation, migration and apoptosis, cell polarity [12]. The comparisons between two disorders are as follows (Table 1).

Cell proliferation in PKD and cancer

ADPKD cells and cancer cells are both characterized by enhanced cell proliferation. Ibrahim et al. found increased rates of proliferation within the epithelium from both cystic and noncystic tubules that were significantly higher than the rates observed in normal kidneys [13], although the process was much slower than that of the tumors.

Ke Sun and Dechao Xu contribute equally to this work.

✉ Changlin Mei
changlinmei@smmu.edu.cn

[1] Department of Nephrology, Kidney Institute, Changzheng Hospital, Second Military Medical University, No. 415 Fengyang Road, Shanghai 200003, China

Table 1 Biological characteristics of ADPKD and cancer

Features	ADPKD	Cancer
Cell proliferation	1. Modest elevation of cell proliferation in cystic epithelium 2. Closely involved in mTOR, cAMP/PKA and mitogenic signaling pathways	1. Unrestricted proliferation 2. Autocrine and paracrine growth stimulation mediated by a pro-proliferative microenvironment
Cell differentiation	1. The polycystins are essential to maintain the differentiated phenotype of the tubular epithelium 2. Primary cilia and EGFR pathway have involved in cell differentiation	The differentiation state of cancer is an important criterion for the classification of solid tumors
Cell migration	ADPKD cells neither invade nor metastasize	1. Tumor intrinsic changes including cell differentiation and polarization 2. Loss of cell–cell/matrix attachment protein
Cell apoptosis	1. Apoptosis found in the cyst epithelia are in low-level 2. Apoptotic factors are found in both induce and attenuate cystogenesis	Apoptosis is an invariably circumstance during tumor progression
Cell polarity	1. Disruptions of cell polarity are found in ADPKD 2. Loss of cell polarity complexes result in cystic kidney	1. Loss of cell polarity is a hallmark of carcinoma 2. The abnormal cell polarity contributes to the progress of tumor growth

It has been reported that the PI3K-AKT-mTOR pathway is activated in several cancers and, in particular, that mTOR plays a key role in cancer cell growth and proliferation [14, 15]. In ADPKD, mTOR is aberrantly activated, and inhibiting mTOR was shown to retard cyst growth in several animal models of PKD [16, 17]. The mTOR pathway can be activated by the ERK pathway in PKD, which is downstream of cAMP/PKA [18]. Thus, the mTOR pathway plays an important role in the cell proliferation between PKD and cancer.

cAMP/PKA pathway is another significantly changed signaling in ADPKD, and the activation of cAMP/PKA signaling pathway plays an important role in cystogenesis, activating proliferative signaling pathways, stimulating chloride and fluid secretion, and inducing interstitial inflammation [19]. To date, Tolvaptan, targeting cAMP/PKA pathway, is the only approved therapeutic medication for ADPKD [20, 21]. Besides, cAMP/PKA is also contributed to cell proliferation in several cancers [22, 23]. Down-regulation of cAMP sensitizes tumor cells for anti-cancer treatment [24].

The similarity between ADPKD and cancer in cell proliferation may relate to the activation of mitogenic signaling pathways. The proliferation of tumor cells is mostly driven by the cell cycle progression, which depends on the binding of cyclin to cyclin-dependent protein kinase (CDK). The transcriptional factor retinal cell tumor protein (p-Rb) plays an important role in cancer cell proliferation; p-Rb can be phosphorylated and thus activated by cyclin D1-Cdk4 and cyclin E-Cdk2. In ADPKD, cyclin D1/Rb is activated and correlated with the proliferation of epithelial cells in cystic kidneys [25].

Besides, the activation of several pro-proliferative signal pathways including the WNT [26, 27], RTKs, EGFR/ErbB1 and HER2/ErbB2 [28, 29], as well as downstream effectors B-RAF, ERK, SRC [30, 31], which have been involved in tumor growth, is associated with ADPKD.

In summary, cell proliferation plays an important role in the processes of tumorigenesis and cystogenesis, and the proliferative signal pathway may be a critical target for the therapy of ADPKD and cancer.

Cell differentiation in PKD and cancer

The change of differentiation state is one of the characteristics of cancer [32]. Besides, the differentiation state of cancer is an important criterion for the classification of solid tumors, because it is an indication of tumor invasiveness and therefore has prognostic significance [33].

The polycystins are essential to maintain the differentiated phenotype of the tubular epithelium [34]. PC1 and PC2 form a complex in primary cilia which have been reported have a role in regulating cell proliferation and differentiation [35–37]. Recently, some studies have found that EGFR signaling pathway play an important role in the regulation of cyst formation in ADPKD [38, 39]. Notably, EGFR pathway have involved in cell differentiation [39]. Some studies find that mutation of PKD1 led to osteoblast differentiation through STAT3 and p38 MAPK signaling [40].

Cell migration in PKD and cancer

Tumor metastasis is a complicated process, and multiple genes are involved in three key steps. In the early stage of tumor metastasis, the expression of cell adhesion molecules such as E-cadherin and integrin, which are involved in cell–cell contact and cell-extracellular matrix interaction, is dysregulated [41, 42]. In the next step, the secretion of proteolytic enzymes by tumor cells or stromal cells

is required, which will degrade the extracellular matrix and the basement membrane of blood vessels [43, 44]. Finally, with the effect of growth factors and chemokines, tumor cells migrate to the target organs [45–47].

E-cadherin is a key mediator of cell–cell adhesion in epithelial tissues [41]. Loss of E-cadherin can enhance tumor invasion and metastasis in many epithelial cell-derived tumors [48]. Several recent studies have shown that PC-1 interacts with E-cadherin, α-catenin, and β-catenin and acts as a mechanical sensor via focal adhesion to the extracellular matrix and cell–cell junctions to transfer extracellular signals into cells [49, 50]. In ADPKD, because of a failure of recruitment by polycystin-1, E-cadherin is trapped in the cytoplasm [51, 52].

Integrin is a cell surface hetero-dimeric glycoprotein that mediates cell-ECM interactions, thereby transferring the extracellular signals into cells to regulate the intracellular actin cytoskeleton, which is important for cell migration [42]. Cell-ECM attachment induces the hetero-dimeric assembly of integrin receptors, leading to the aggravation of the COOH ends of intracellular β1-integrin, which recruits multiple structural and signal proteins to form a multi-molecular binding complex [53, 54]. Structural proteins, such as talin, troponin, deoxynucleotides, and β-actin, as well as signaling proteins like focal adhesion kinase (FAK), c-Src, p130cas, and puerarin are involved in the formation of this multi-molecular binding complex [55, 56]. Down-regulation of β1-integrin or members of this multi-molecular binding complex impairs tumor cell migration [57, 58]. It has been reported that PC-1 forms a complex with β1-integrin and other adhesion proteins in the renal epithelial cells, and dysfunction of PC-1 induces β-catenin shifting from the cell membrane to the nucleus [59, 60]. In addition, it has been reported that the low intracellular calcium concentration in ADPKD cells leads to high levels of MYC expression, which can inhibit cancer metastasis by suppressing the silencing of αv and β3 integrin subunits at the transcriptional level [61]. In addition, Boca et al. found that PC-1 induces cell migration by regulating phosphatidylinositol 3-kinase-dependent cytoskeletal rearrangement [62]. Several lines of evidence have indicated that PC-1 induces cell migration by regulating intracellular actin-induced cell skeleton remodeling, and PC-1 abnormalities impair the directional migratory ability of renal epithelial cells and thus promote the formation of cysts [63, 64]. Therefore, PC-1 abnormalities in ADPKD may inhibit tumor metastasis by reducing the capability of cell migration.

As is known, compared with cancer, ADPKD cells neither invade nor metastasize, and understanding the different natures of ADPKD and cancer may help reduce the incidence of cancer by preventing tumor growth and metastasis.

Cell apoptosis in PKD and cancer

Apoptosis is a process of programmed cell death and is dysregulated in PKD and cancer [65–67]. During the multistage carcinogenesis, many genes triggering apoptosis are down-regulated, and many apoptosis-suppressing genes are up-regulated, leading to tumor cell clonal formation and tumor growth [68–70]. Thus, the selective promotion of tumor cell apoptosis is a strategy for cancer therapy.

Several studies have shown that the apoptosis of tubular and cystic epithelial cells is enhanced in kidneys from many animal models of ADPKD and from ADPKD patients [71–73]. However, according to Fan et al, merely low levels of apoptosis are typically discovered during renal cyst formation [74]; in addition, increased apoptosis is an early event in cyst development in ADPKD [13]. Furthermore, some evidence suggests that the loss of Bcl-2, an anti-apoptotic regulator, might induce cyst growth through a different mechanism than that induced by loss of Pkd1. By contrast, apoptosis may be the main culprit for the loss of renal tissue and function, and Bcl-2 knock-out mice exhibit an induced aggressive development of renal cysts [75].

Therefore, there are marked differences between ADPKD and cancer in the process of apoptosis, and the effect of apoptosis blockage on ADPKD progression is still controversial.

Cell polarity in PKD and cancer

Epithelial cell polarity is essential for the establishing and maintaining morphological and functional asymmetries of normal renal structure and function, and the appropriate membrane polarization of ion and fluid transporters, channels, and receptor proteins is essential for normal epithelial function and requires the appropriate integration of several cellular processes [76]. Epithelial cell polarity is maintained by three conservative polarity complexes, namely, PAR [77], Crumbs [78], and SCRIB [79]. Conserved signal mechanisms such as TGFβ and Integrin signal regulate the formation and maintenance of polarity of epithelial cells. Dissolution of tight junction and loss of polarity is a hallmark for carcinoma.

The abnormal cell polarity in ADPKD includes the mis-polarization of normal basal membrane proteins to apical, such as epidermal growth factor receptors (EGFR) and $Na^{+-}K^{+}$-ATPase α1 subunit; the mis-polarization of normally apical membrane proteins to basolateral membranes includes the Na^{+}-K^{+}-$2Cl^{-}$ (NKCC1) symporter; and the failure to traffic and insert proteins into membranes resulting in their intracellular accumulation, such as E-cadherin and the β1 subunit of Na^{+}-K^{+}-ATPase. Abnormalities in polarity complexes in ADPKD epithelial include loss of E-cadherin, and focal adhesion kinase (FAK), MALS-3, Crumbs and

DLG complexes, as well as disruptions in Rab/sec, syntaxin trafficking, and membrane docking pathways. Moreover, the mutation of several cell polarity complexes would result in cystic kidney, indicating the essential role of cell polarity in cyst formation of ADPKD [80–82].

The establishment and maintenance of epithelial cell polarity are essential for normal kidney development and differentiation to prevent abnormal cystic dilation, therefore interventions to reverse polarity defects to normal would provide treatment opportunities for ADPKD and cancer.

The relationship between PKD and cancer

Cyst growth in PKD has many parallels with cancer; however, the exact relation between ADPKD and cancer has never been confirmed. Several cohorts and large case series studies have investigated the risk of cancer in patients with PKD, but the results are controversial (Table 2).

Walters and Braasch [83] first reported the association between renal cell carcinoma (RCC) and autosomal dominant polycystic kidney disease in 1934. They thought that ADPKD patients may have a high risk of developing RCC because several RCC-related risk factors were observed in these patients, such as cluster-like papillary hyperplasia in the polycystic kidney, which is a precancerous lesion for RCC [84]. Hajj et al. reviewed 79 nephrectomized patients with ADPKD and chronic kidney failure (CRF) in their department between 1982 and 2003 [85] and found that ADPKD in patients who progressed to CRF was associated with a high incidence of RCC (8.3%); the incidence of RCC increased to 12% in patients after one year of dialysis or renal transplantation. However, Denton et al found that the incidence of RCC in ESRD patients who accepted transplantation was only 4.2% [86], so the incidence of RCC in ADPKD patients was 2 to 3 times more frequent than that in patients with ESRD alone. Although the researchers did not have sufficient data to account for adequate confounding factors, we still believe that ADPKD is associated with an increased frequency of RCC according to the reported multiple cases, which means that it is of great importance for clinicians to maintain a high index of suspicion for RCC in such patients.

In addition to these case series studies, two large-scale studies have analyzed whether ADPKD patients have an increased risk of cancer; however, their results are contradictory. An epidemiological study based on the data from the SRTR (Scientific Registry of Transplant Recipients) compared the cancer incidence in non-ADPKD patients and ADPKD patients after receiving renal transplantation [87] and with a mean follow-up time of 4.12 years and 3.64 years, respectively. The results showed that the ADPKD group had a lower cancer incidence than did the non-ADPKD group.

Table 2 Clinical trials about the association of ADPKD and cancer

Clinical research	Results	Limitations
Research from the Departments of Urology and Histopathology (85, 86)	The incidence of RCC in ADPKD patients with ESRD would be 2–3 times more frequent than in patients with ESRD alone	1. They did not account for adequate confounding factors 2. No data about the incidence of cancer in ADPKD without ESRD
Data from the Scientific Registry of Transplant Recipients (87)	After multivariable adjustment, the cancer incidence was lower in PKD recipients than in others	Enrolled patients are following renal transplantation; thus, the cancer incidence is still unknown for ADPKD without renal transplantation
A large cohort study conducted in Taiwan (93)	ADPKD patients, when compared with non-PKD patients, have a higher cancer incidence, particularly for liver cancer, colon cancer, and kidney cancer	Some of the habits of patients, such as smoking, BMI, and other factors associated with cancer, were not considered

The investigators thought this association arises because ADPKD recipients are more likely to have nephrectomies than are their non-ADPKD counterparts and suggested that ADPKD may have an intrinsic cellular mechanism against cancer. However, there are some limitations to this study. One important limitation of concern was that this study was performed on patients following renal transplantation; thus, the cancer incidence is still unknown for ADPKD and non-ADPKD patients who do not receive renal transplantation and have a similar renal function. In addition, many low-frequency cancers occur infrequently in ADPKD recipients, so some of the estimates are unstable.

Another large cohort study was conducted in Taiwan to evaluate the relationship between cancer and ADPKD [88], in which 4346 ADPKD patients and 4346 non-ADPKD patients were included in the study from 1998 to 2011. The mean follow-up was 3.72 years for ADPKD patients and 4.96 years for non-ADPKD patients. This study showed that ADPKD patients compared with non-PKD patients have a higher cancer incidence, particularly for liver cancer, colon cancer, and kidney cancer. After adjustment for all potentially confounding factors (e.g., age, sex, comorbidities of hypertension), the risk of cancer remained higher in the polycystic kidney disease cohort than in the non-polycystic kidney disease cohort (adjusted SHR 1.98, 95% CI 1.69–2.31; <0.0001). There are some limitations in this study; for example, some of the habits of patients, such as smoking, BMI, and other factors associated with cancer, were not considered, and the administration of pharmaceutical agents such as antidiuretic and ACEI drugs may affect the cancer incidence in ADPKD patients. Nevertheless, the results show a higher risk of cancer in patients with PKD than in those without this disease after completely excluding cases with chronic kidney disease or ESRD, which supports the hypothesis that the typical renal cystic changes in patients with ADPKD are a precursor of neoplasia. Therefore, when treating patients withADPKD, health-care professionals need to be aware of the risk of cancer.

The treatment in ADPKD and cancer

The broad similarities and associations between ADPKD and cancer cells suggest that many drugs that slow the progress of tumors would have similar effects in ADPKD. However, ADPKD is much less lethal than many forms of cancer, and that the treatments of cancers have toxic adverse effects that would limit their application in ADPKD patients. Hence, the safety and tolerability of targeted cancer drugs should be considered in the treatment of ADPKD. Some early evidences indicate that inflammation and macrophage infiltration contribute to ADPKD pathogenesis, which suggests that anti-inflammatory drugs targeting macrophages or inflammatory components may be a well-tolerated strategy for long-term relief of cystic growth [89, 90]. Notably, given the already impaired renal function of patients with ADPKD, it will be critical to avoid agents that are nephrotoxic.

Overall, the many commonalities and associations between ADPKD and tumor make it possible that treatment strategies developed for one disease might be applicable to the other. For example, AMPK activity is reduced in both ADPKD and RCC and activation of AMPK by metformin can provide therapeutic benefit in both diseases [91, 92]. In the future, we hope the treatment of ADPKD and cancer can benefit from each other.

Conclusion

With the improved understanding of the signal and pathological characteristics of ADPKD, marked similarities and associations between ADPKD and cancer have been revealed. As mentioned above, increased cell proliferation, abnormal cell differentiation, and disruption of cell polarity have been obviously observed in cancer and ADPKD. Alternatively, the major differences between ADPKD and cancer, involving apoptosis and cell metastasis, may explain the lower morbidity and mortality of ADPKD. Not only benefit the treatment of ADPKD, but we can also deepen our understanding of cancer biology through this comparative analysis. Many therapies that slow the proliferation of tumors would have similar effects in limiting the proliferation of ADPKD cells. However, many anticancer treatments have toxic adverse effects that would limit their application in ADPKD and the already impaired renal function of ADPKD patients should be taken into consideration. In addition, future studies can focus on the biological features of ADPKD, combining the presence of proliferation and the absence of metastasis, which will be helpful to the therapy of cancer. Whether ADPKD patients have an increased risk of cancer is still under discussion. However, according to our analysis of current clinical studies, we highly recommend that clinicians be on high alert for suspicion of cancer in ADPKD patients.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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