Chapter 3
Cell Proliferation and Apoptosis in ADPKD

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Abstract Increased tubular epithelial cell proliferation with fluid secretion is a key hallmark of autosomal dominant polycystic kidney disease (ADPKD). With disruption of either *PKD1* or *PKD2*, the main causative genes of ADPKD, intracellular calcium homeostasis and cAMP accumulation are disrupted, which in turn leads to altered signaling in the pathways that regulate cell proliferation. These dysregulations finally stimulate the development of fluid-filled cysts originating from abnormally proliferating renal tubular cells. In addition, dysregulated apoptosis is observed in dilated cystic tubules. An imbalance between cell proliferation and apoptosis seems to contribute to cyst growth and renal tissue remodeling in ADPKD. In this section, the mechanisms through which cell proliferation and apoptosis are involved in disease progression, and further, how those signaling pathways impinge on each other in ADPKD will be discussed.

Keywords Apoptosis • Proliferation • Autosomal dominant polycystic kidney disease • ADPKD

3.1 Cell Proliferation in ADPKD

Cell proliferation is an important intracellular process in which nearly all of the billions of cells in our body undergo in a strictly regulated manner. It allows cell populations to increase through cell growth and division. Mechanisms that regulate cell proliferation include cell cycle controls and series of protein kinase cascades stimulated by various growth factors. The cell cycle mainly controls cell division and it can be divided into four stages: the G1, S, G2, and M phases. DNA replication and the duplication of identical sets of chromosomes occurs during S phase. Cell division finally occurs in M phase and involves DNA packing and chromosome segregation. Gap phases between the S and M phases involve preparation for the following

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stages and the determination of whether to proceed to the next stage. The cell cycle is mainly mediated by cyclin-dependent kinases (CDKs), which are positive regulators of the cell cycle, and their inhibitors. Those proteins control cell cycle through switching the activity of specific proteins on and off by phosphorylation at appropriate time points in the cell cycle (Mitchison 2003). Not only cell cycle control, but also several signaling pathways mediated by series of protein kinases are well-characterized mechanisms regulating cell proliferation. One of the best understood signaling pathways of the mitogen-activated protein kinases (MAPKs) is the extracellular signal-regulated kinase (ERK) pathway. Binding of growth factors or cytokines to their cognate receptors sequentially activates MAPKs in a multi-step process. Signaling occurs through a cascade of protein kinases including B-Raf, mitogene-activated protein kinase kinase (MEK), and ERK. Ultimately, phosphorylated ERK translocates to the nucleus and activates transcription factors, thereby altering gene expression to stimulate cell proliferation (Zhang and Liu 2002). Another mechanism by which protein kinases influence the control of cell growth is via the mammalian target of rapamycin (mTOR) signaling pathway, which can be stimulated by extracellular factors including growth factors. When it is activated, mTOR phosphorylates the serine/threonine protein kinase Akt and finally leads to enhanced cell proliferation (Dobashi et al. 2011).

In normal tissues that are fully differentiated, cell proliferation rarely occurs; in such tissues the cells each have their own specialized function and no longer actively divide. Therefore, cell proliferation is tightly controlled and it is highly restricted to cells that mediate replenishment of the tissues under specific conditions, such as following physical injuries. Uncontrolled cell proliferation is abnormal in terminally differentiated tissues and is commonly observed in human diseases including a number of cancers (Evan and Vousden 2001), as well as being a characteristic hallmark of ADPKD.

3.1.1 Aberrant Calcium Signaling and Cell Proliferation in ADPKD

Polycystin-1 (PC1) and polycystin-2 (PC2), which are encoded by *PKD1* and *PKD2*, respectively, are localized in the primary cilia. PC1 and PC2 form a polcystin complex and function as a mechanosensor, translating mechanistic stimuli into calcium signaling. Specifically, PC2 acts as a nonselective cation channel and regulates the intracellular calcium level by transporting calcium into the cell (Gonzalez-Perrett et al. 2001). PC1, which is a large integral membrane receptor, interacts with PC2 and regulates its activity. Polycystin complex not only works in the cilia, but it can also regulate the intracellular calcium level by transporting calcium across the endoplasmic reticulum (ER) membrane. PC2, which is located on the ER membrane, stimulates inositol trisphosphate receptor (IP3R), leading to calcium release from the ER into the cytoplasm (Li et al. 2005). PC1, on the other hand, reduces the

intracellular calcium level via inhibiting the interaction of PC2 with IP3R (Santoso et al. 2011). Above all, the disruption of polycystin complex proteins impairs intracellular calcium homeostasis, which leads to the alteration of various signaling pathways. The consequences of this include abnormally hyper-activated cell proliferation and fluid secretion, which leads to the expansion of renal cysts (Harris and Torres 2009).

Reduced intracellular calcium caused by defects in polycystin complex proteins primarily leads to cyclic adenosine monophosphate (cAMP) accumulation (Yamaguchi et al. 2004; Chebib et al. 2015). Previous studies revealed that calcium restriction is involved in both the synthesis and hydrolysis of cAMP. A low level of calcium stimulates the enzyme that catalyzes cAMP formation, adenylyl cyclase 6, which is essentially inhibited by calcium. Besides, the hydrolysis of cAMP is reduced via the inhibition of calcium-calmodulin dependent phosphodiesterases as a result of a low level of intracellular calcium (Wang et al. 2010). cAMP can also be modulated by circulating vasopressin. A high urinary concentration of vasopressin, which is commonly observed in ADPKD, increases the intracellular level of cAMP, mediated by vasopressin V2 receptor activation (Wang et al. 2008).

The accumulation of intracellular cAMP stimulates the cAMP-dependent B-Raf/MEK/ERK signaling pathway, which is one of the key regulators of cell proliferation (Yamaguchi et al. 2004). Hyper-activated ERK also affects the up-regulation of the mTOR signaling pathway, another representative pathway regulating cell proliferation, via the inhibition of tuberous sclerosis complex (TSC1/2) (Yamaguchi et al. 2003). Moreover, the activity of cAMP response element binding protein (CREB) is increased by cAMP and causes the over-expression of the epidermal growth factor (EGF)-like peptide amphiregulin, thereby leading to increased cell proliferation in an EGF receptor-dependent manner. CREB is also sequentially involved in the Raf/MEK/ERK pathway.

On the other hand, calcium influx can also be regulated by other heteromultimeric channels, including PC2/TRPC1 and PC2/TRPV4. Those channels are also localized on the cilia and transduce calcium into cells in response to fluid-flow (Bai et al. 2008). However, defects in either TRPC1 or TRPV4 do not lead to ADPKD, suggesting that an abnormal level of intracellular calcium is not the only relevant factor for triggering the development of renal cysts. Instead, the onset of ADPKD must be closely linked to dysfunctions in either PC1 or PC2, which are the main causative proteins of the disease (Ma et al. 2013).

3.2 Regulation of Cell Proliferation by Polycystins in Renal Primary Cilia

Cell proliferation is able to be regulated by polycystins directly as well as indirectly via a low intracellular calcium level.

First, PC1 inhibits the mTOR activity of normal renal epithelial cells via modulating the stability of TSC1/2, the negative regulator of mTOR (Distefano et al. 2009). The signaling pathway mediated by mTOR plays a central role in cell proliferation in response to growth factors including EGF and insulin-like growth factor 1. The activation of phosphatidylinositide 3-kinases followed by the stimulation of growth factor receptors leads to the sequential phosphorylation of protein kinase B (also known as Akt) and mTOR complex. Activated mTOR complex positively regulates protein synthesis (which finally allows enhanced cell proliferation) by the up- or down-regulation of ribosomal protein S6 kinase beta-1 or eukaryotic translation initiation factor 4E-binding protein 1, respectively. GTP-bound active Rheb, which is one of the subtypes of the Ras superfamily, is required in this process (Ruvinsky and Meyuhas 2006; Long et al. 2005; Laplante and Sabatini 2009). TSC1/2 complex inhibits the activation of Rheb. Therefore, the up-regulation of TSC1/2 by PC1 blocks mTOR activation and finally leads to the inhibition of cell proliferation in normal renal epithelia.

Another mechanism by which PC1 negatively regulates cell proliferation in normal conditions is through control of the cell cycle process. PC1 directly activates the Janus kinase and signal transducer and activator of transcription signaling pathway, leading to an increased expression of p21Waf1. p21Waf1 is a CDK inhibitor that causes cell cycle arrest in G0/G1 phase when it is expressed at a high level. A functionally intact interaction of PC1 with PC2 is necessary in this process, and mutations in PC1 or PC2 that affect the function of these proteins or inhibit their binding to each other usually results in dysregulated cell growth (Bhunia et al. 2002).

PC2 negatively regulates cell proliferation not only via its interaction with PC1, but also independently of PC1 via modulating the pancreatic ER-resident eukaryotic initiation factor 2 (eIF2) alpha kinase (PERK)-eIF2 phosphorylation signaling pathway. eIF2 is required to initiate translation by mediating the binding of tRNA to the ribosome, and through this activity it ultimately regulates cell growth control. The activity of eIF2 can be regulated by several factors including PERK, which is essentially induced by ER stress (Joshi et al. 2013). PC2 functions as a PERK-activating factor. It is physically localized within the PERK-eIF2 protein complex and it enhances eIF2 phosphorylation by PERK, which finally leads to restricted cell proliferation (Liang et al. 2008).

Altogether, in ADPKD, which is mainly caused by a defect in either PC1 or PC2, an abnormal increase of cell proliferation caused by several mechanisms is a hallmark of the disease. The inhibition of calcium influx that results from dysfunctions in the PC1-PC2 complex increases intracellular cAMP accumulation by both enhanced cAMP synthesis and reduced cAMP hydrolysis. This deficit in calcium transport directly or indirectly stimulates the Raf/MEK/ERK signaling pathways and finally leads to abnormally enhanced cell proliferation. Moreover, PC1 and PC2 essentially have roles in the blockade of cell proliferation via the regulation of key factors for cell proliferation. Thereby, the malfunction of either PC1 or PC2 results in increased cell proliferation. Indeed, the onset of ADPKD must be tightly related to hyper-activated cell proliferation.

3.3 Apoptosis in ADPKD

Apoptosis is a process of programmed cell death that eliminates damaged cells. Whereas necrosis is not uniformly regulated, apoptosis is highly controlled by its regulators and undergoes defined sequential changes in morphology. These changes include a reduced cell volume, membrane blebbing, and loss of cellular membrane asymmetry, as well as nuclear fragmentation, chromatin condensation, and DNA fragmentation. During this process, phosphatidylserine is exposed at the surface of the cell and promotes the phagocytosis of the apoptotic cell by immune cells (Elmore 2007). The major regulators of apoptosis are the caspases and inhibitor of apoptosis proteins (IAPs). Caspases, which are cysteine proteases, exist in the cytoplasm as inactive forms in normal cells. Upon the activation of apoptosis, caspases are transformed into their functional forms via two serial cleavage steps and initiate apoptosis (Wolf and Green 1999). IAPs are the natural inhibitors of caspases and they antagonize apoptosis through inhibiting the action of caspases as well as regulating cell division. There are two representative activation mechanisms of apoptosis, which are known as the extrinsic and intrinsic pathways. The intrinsic pathway, also known as the mitochondrial pathway, is mainly induced by increased cytochrome c release from mitochondria. Cytochrome c interacts with apoptosis protease-activating factor-1 to serially recruit caspases including caspase-9, caspase-3, and caspase-7; thereby, apoptosis signaling is initiated. In the extrinsic pathway, extracellular factors, rather than cytosolic ones, are involved in the initial step of apoptosis activation. After the binding of ligands to death receptors (such as the FAS-FAS receptor), caspases are recruited and cleaved into their active forms followed by their recruitment by adaptor proteins. The caspase that mainly mediates extrinsic apoptosis is caspase-8, and it sequentially activates other caspases, resulting in an activation cascade (Ashkenazi and Dixit 1998; Portt et al. 2011). Apoptosis regulated both by intrinsic and extrinsic mechanisms has a critical role in normal kidney development and its dysregulation has been reported to be related to various types of renal diseases including cancer and ADPKD (Goilav 2011).

3.3.1 Altered Regulation of Apoptosis During ADPKD Pathogenesis

The dysregulation of apoptosis is commonly observed in rodent models of ADPKD. First, apoptosis has been reported to be up-regulated in the Han:SPRD rat model, which is derived from a spontaneous mutation in the Sprague–Dawley strain and has polycystic kidney disease (PKD) phenotypes. Homozygous animals that aggressively develop renal cysts have shown increased activities of apoptosis-inducing factors including caspases (specifically caspase-3, caspase-7, caspase-8, and caspase-2) as well as enhanced cytochrome c release from mitochondria into the cytoplasm (Tao et al. 2005). Conversely, PKD phenotypes have appeared in

rodent models that have either an increased or decreased genetic expression of apoptosis-related genes. Transgenic mice targeting c-Myc, a proto-oncogene that is involved in cell proliferation and apoptosis, have been found to develop polycystic kidneys. These mice finally develop end-stage renal disease and die of renal failure (Lanoix et al. 1996). Besides, an in vivo model that has a genetic knock-out of pro-apoptotic Bcl-2 also showed PKD phenotypes and hyper-activation of cell proliferation and apoptosis (Veis et al. 1993; Sorenson et al. 1996). Interestingly, the level of those PKD-causing apoptosis related genes turned out to be increased in ADPKD, while others including Bax and P53 were unchanged (Lanoix et al. 1996). Other observations of human ADPKD have shown that increased apoptosis is specifically detected only in the renal epithelial tubules of the non-cystic region in patient tissues. Indeed, apoptosis may be involved in the loss of normal nephrons, leading to the destruction of renal architecture, rather than having a major role in cyst development (Woo 1995).

Assertions for the role of apoptosis in ADPKD are controversial (Zhou and Kukes 1998). Some consider dysregulated apoptosis to be one of the main causes of ADPKD, whereas others have proposed that apoptosis may delay disease progression. Clearly, the hyper-activation of cell proliferation, which is caused by increased intracellular cAMP followed by the inhibition of calcium influx due to the dysfunction of the PC1-PC2 complex, is the core factor for ADPKD onset. However, it is evident that abnormal apoptosis has also been reported in several studies; thereby, the failure to maintain a proper balance between proliferation and apoptosis seems to be important in progression of ADPKD (Ecder et al. 2002).

3.4 Therapeutic Approaches Targeting Cell Proliferation or Apoptosis

No specific therapies or medications are available to prevent or delay ADPKD progression yet. However, there have been several trials of therapies targeting either cell proliferation or apoptosis, which are the main causative mechanisms inducing cyst growth and fluid secretion (LaRiviere et al. 2015; Riella et al. 2014). V2 receptor antagonists are one drug that has been investigated as a therapy for ADPKD. V2 receptor is stimulated by vasopressin, and intracellular signaling pathways mediated by vasopressin-V2 receptor signaling are highly involved in cAMP generation. In pre-clinical attempts, ADPKD rodent models treated by antagonists targeting V2 receptor showed alleviated disease progression (Gattone et al. 2003; Torres et al. 2004; Wang et al. 2005). Another trial drug targeting the cAMP signaling pathway was somatostatin analogs. Essentially, somatostatin binds with several G-protein coupled receptors (GPCRs) and thereby maintains low cAMP levels via the regulation of ACs activity. It also down-regulates cell proliferation and the secretion of hormones or growth factors. Therefore, somatostatin analogs lowered intracellular cAMP, which finally leads to attenuated cystogenesis followed by the down-regulation of cell proliferation, in preclinical studies using rodent models with renal cysts

(Masyuk et al. 2007; Masyuk et al. 2013). Besides, inhibitors targeting the mTOR signaling pathway, which is a major mechanism regulating cell proliferation, have been shown to effectively attenuate PKD phenotypes including renal enlargement and development of the cysts (Wahl et al. 2006) through in vivo studies. Pre-clinical trials of drugs targeting apoptosis have been attempted relatively less frequently than those of drugs targeting cell proliferation. The down-regulation of apoptosis followed by caspase inhibition has revealed alleviated PKD progression in a rodent model with renal cysts. Additionally, a drug that directly targets the potential apoptosis-inducing factor CDK5 was indeed shown to inhibit cystic phenotypes in a rodent model of PKD (Bukanov et al. 2006; Ibraghimov-Beskrovnaya 2007).

3.5 Summary

In summary, the hyper-activation of cell proliferation is a key phenotype that initiates and accelerates the progression of ADPKD. It could be explained by two major mechanisms. The first mechanism is cAMP accumulation followed by lowered calcium influx, which stimulates the activities of cell proliferation-related proteins including B-Raf/MEK/ERK and mTOR. The second mechanism is the loss of the anti-proliferative functions of PC1 and PC2 through defects in either protein caused by gene mutations. The role of excessive cell proliferation in ADPKD has been clearly characterized and pre-clinical trials of drugs targeting cell proliferation have reported the effective attenuation of disease progression. On the other hand, the role of apoptosis in ADPKD pathogenesis is not yet fully understood. Apoptosis regulators including caspases have recently been reported to show increased activity in ADPKD rodent models, and indirectly targeting apoptosis in pre-clinical studies has been found to delay disease onset. Besides, renal failure followed by cysts development has been commonly observed in mice with defective apoptosis. Taken together, those findings suggest that apoptosis seems to be involved in the pathogenesis of ADPKD, associated either with cysts enlargement or the remodeling of kidney structure. Altogether, the failure to maintain an appropriate balance between cell proliferation and apoptosis appears to be an important driver of ADPKD progression. Therefore, specifically targeting proliferation and/or apoptosis could be an effective therapeutic strategy.

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