# Chapter 5
# Polycystic Kidney Disease and Renal Fibrosis


**Cheng Xue and Chang-Lin Mei**

**Abstract** Polycystic kidney disease (PKD) is a common genetic disorder characterized by formations of numerous cysts in kidneys and most caused by PKD1 or PKD2 mutations in autosomal dominant polycystic kidney disease (ADPKD). The interstitial inflammation and fibrosis is one of the major pathological changes in polycystic kidney tissues with an accumulation of inflammatory cells, chemokines, and cytokines. The immune response is observed across different stages and occurs prior to or coincident with cyst formation in ADPKD. Evidence for inflammation as an important contributor to cyst growth and fibrosis includes increased interstitial macrophages, upregulated expressions of pro-inflammatory cytokines, activated complement system, and activated pathways including NF-κB and JAK-STAT signaling in polycystic kidney tissues. Inflammatory cells are responsible for overproduction of several pro-fibrotic growth factors which promote renal fibrosis in ADPKD. These growth factors trigger epithelial mesenchymal transition and myofibroblast/fibrocyte activation, which stimulate the expansion of extracellular matrix (ECM) including collagen I, III, IV, V, and fibronectin, leading to renal fibrosis and reduced renal function. Besides, there are imbalanced ECM turnover regulators which lead to the increased ECM production and inadequate degradation in polycystic kidney tissues. Several fibrosis associated signaling pathways, such as TGFβ-SMAD, Wnt, and periostin–integrin-linked kinase are also activated in polycystic kidney tissues. Although the effective anti-fibrotic treatments are limited at the present time, slowing the cyst expansion and fibrosis development is very important for prolonging life span and improving the palliative care of ADPKD patients. The inhibition of pro-fibrotic cytokines involved in fibrosis might be a new therapeutic strategy for ADPKD in the future.

**Keywords** Polycystic kidney disease · Inflammation · Extracellular matrix · Fibrosis

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## 5.1 Introduction

Polycystic kidney disease (PKD) is a genetic disorder which is characterized by the formations of cysts in both kidneys and other organs. PKD can be divided into two forms according to genetic pattern, autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). ARPKD affects approximately 1/20,000 individuals (Bergmann 2017). Its causative gene is PKHD1 which encodes fibrocystin/polyductin. ADPKD affects about 1/1000 individuals (Wuthrich and Mei 2012; Xue et al. 2016). PKD1 and PKD2 are mainly two pathogenic genes which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Dysfunctional proteins of PC1/2 or fibrocystin influence the function of the primary cilia (Zimmerman and Yoder 2015), which is involved in mechanosensation to detect the fluid flow passing through the tubule lumen and regulate cell proliferation, oriented cell division, as well as cell polarity (Zimmerman and Yoder 2015). Because ADPKD is more common than ARPKD, the data about ADPKD and fibrosis is abundant, this chapter only focuses on ADPKD.

Cyst growth in ADPKD is associated with increases in epithelial cell proliferation, dedifferentiation, and fluid secretion. The enlargement of cysts leads to the compression and obstruction of surrounding nephrons which could significantly decrease the kidney function (Xue et al. 2018). At the late stage of ADPKD, cyst formation is always accompanied by extracellular matrix (ECM) deposition and fibrosis formation (Grantham et al. 2011). Fibrosis is characterized by excessive productions of collagen accompanied by decompositions of connective tissues. Fibrosis further reduces the renal function and eventually leads to end-stage renal disease (ESRD) (Grantham et al. 2011). Experimental studies found that disruptions of polycystins or primary cilia are associated with inflammation and fibrosis in a variety of polycystic kidney models (Song et al. 2017). In general, increased inflammation and fibrosis aggravates the disease progression. While inflammation and fibrosis are not primary causes of ADPKD, several cells like macrophages and molecules like transforming growth factor (TGF) β related to inflammation and fibrosis can influence renal function and ADPKD progression (Liu et al. 2014; Song et al. 2017).

## 5.2 Inflammation in ADPKD

Inflammation is an important process prior to or coincident with fibrosis in ADPKD (Fig. 5.1) (Harms et al. 2018). The immune response is observed across different stages of ADPKD progression. Perhaps the earliest immune changes are triggered by the loss of PC1/2 function, which may occur before the inflammation pathway activation by renal injury in ADPKD (Karihaloo et al. 2011).

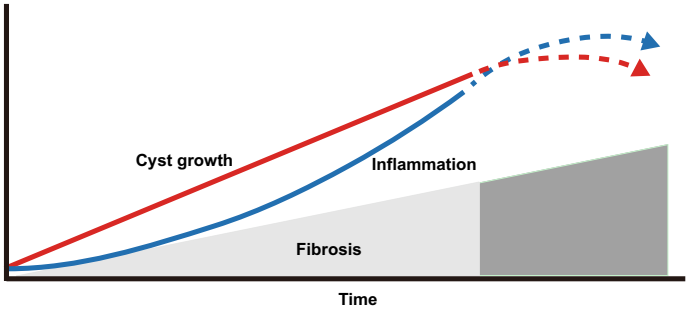


**Fig. 5.1** Changes in renal cystic growth, fibrosis, and inflammation over time. Renal cystic growth increases over time in human studies (solid line). The kidney volume does not increase or may decrease in late stages, while the tissue becomes progressively more fibrotic in some animal studies (dashed line). Abnormal immune inflammation increases over time (solid line). However, in late stages, the progression magnitude of some immune responses may decrease due to the loss of functional renal parenchyma (dashed line)

### *5.2.1 Inflammatory Cells in ADPKD*

Renal interstitial inflammation infiltrate is one of the most notable characteristics of ADPKD (Fig. 5.2). Among the inflammatory cells, macrophage is the most extensively studied cell. Macrophages consist of heterogeneous cell types which play specific roles in ADPKD progression (Karihaloo et al. 2011). Macrophage is involved in innate immunity, tissue development, repair, and homeostasis. Intriguingly, macrophages could become polarized and express pro-inflammatory or anti-inflammatory cytokines in response to signals in the tissue microenvironment (Gordon and Taylor 2005). On one hand, macrophages stimulated with interferon-γor LPS demonstrate a pro-inflammatory Th1-like phenotype, which is referred to as M1-like macrophage. M1 macrophage is characterized by expression of iNOS, interleukin (IL) 1β, and TNF-α (tumor necrosis factor α) (Sica and Mantovani 2012). On the other hand, macrophages treated with IL 4 or 13 produce an anti-inflammatory response and are referred to as M2-like macrophages. M2 macrophages express arginase 1 (Arg1) and IL10 and have wound healing and anti-inflammatory functions (Sica and Mantovani 2012). However, in vivo studies found that macrophages display a range of phenotypes that fall somewhere between the M1 and M2 spectrums and were able to rapidly switch the phenotypes based on external cues. The tissue microenvironment influenced the macrophage polarization (Swenson-Fields et al. 2013). For instance, M1 macrophages could transit into M2 like polarization following phagocytosis of apoptotic and necrotic cells or when cultured with renal epithelial cells.

In normal kidney, nearly half of the resident macrophages derive from the yolk sac while the rest derive from the hematopoietic lineage (Schulz et al. 2012). Resident macrophages play important roles in producing cytokines and monitoring surrounding cells in kidney. The second distinct source of macrophages is the infiltrating macrophage, which rapidly accumulate in response to kidneys injury (Schulz et al.

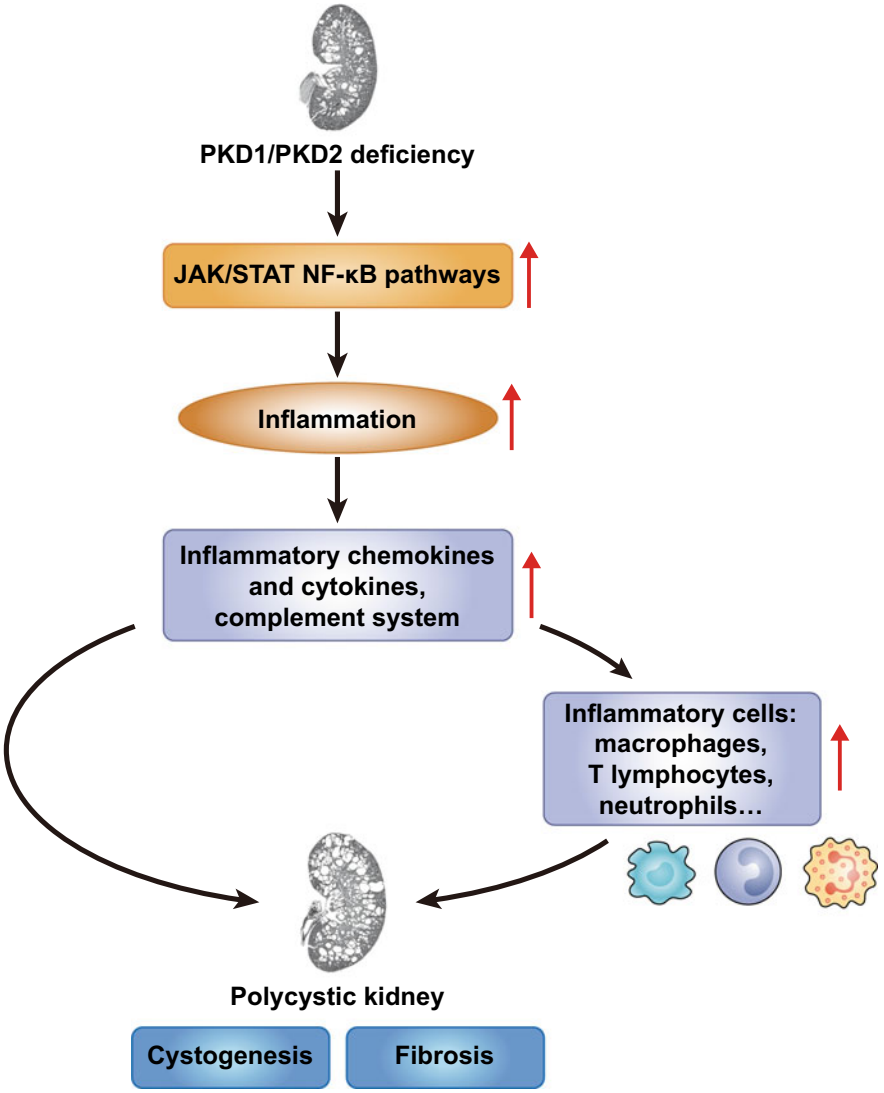


**Fig. 5.2** A schematic summary of inflammation in ADPKD

2012). Infiltrating macrophages could produce pro-inflammatory cytokines and are associated with kidney injury and fibrosis.

Both resident and infiltrating macrophages increase in polycystic kidney tissue (Swenson-Fields et al. 2013). In rodent models, inflammatory cells including macrophages were present prior to or coincident with cyst initiation, and macrophages played important roles in promoting cyst formation (Bastos et al. 2009). Karihaloo et al. found that infiltrating macrophages contributed to the proliferation of

the cystic lining cells (CLCs) and the progression of ADPKD in murine models (Karihaloo et al. 2011). They also verified that primary cyst epithelial cells from ADPKD promoted macrophages converting to the M2-like phenotype (Karihaloo et al. 2011). On the contrary, macrophage depletion using clodronate showed the reduction of cyst growth by influencing cell proliferation in ADPKD. Harris et al. established a model for the contribution of macrophages to PKD progression and regarded activated macrophages as a treatment target in ADPKD (Harris and Torres 2014). Recently, we revealed an interaction between macrophages and CLCs which promoted cyst growth in Pkd1−/− mice through the arginine-polyamine metabolic pathway (Yang et al. 2018). Arg1-encoded protein, arginase-1, was predominantly expressed in macrophages in a time-dependent manner in ADPKD (Yang et al. 2018). Multistage macrophage depletion verified that macrophages expressing high arginase-1 levels accounted for late-stage cyst enlargement, and inhibiting arginase-1 activity significantly retarded cyst growth and effectively lowered the cyst enlargement (Yang et al. 2018). In vitro experiments found that macrophages stimulated CLCs proliferation, and L-lactic acid, primarily generated by CLCs, significantly increased arginase-1 expression and polyamine synthesis in macrophages (Yang et al. 2018). Therefore, arginase-1 secreted by macrophages may be a key molecule involved in cyst formation process and may be a potential therapeutic target to delay ADPKD progression.

The involvement of other inflammatory cells like T lymphocytes, neutrophils, dendritic cells, and mast cells has been reported in ADPKD. The number of CD4-positive T cells was increased in the interstitial tissue of ADPKD (Zeier et al. 1992). Mast cells were found to be involved in PKD progression through the production of pro-inflammatory factors including chymase and Ang II (McPherson et al. 2004). Furthermore, elevated neutrophils were reported in human and canine PKD models (Bernhardt et al. 2007). While a wide variety of inflammatory cells increased in polycystic kidney tissue, future studies should focus on better understanding the respective roles of these cells in cyst formation and fibrosis.

### *5.2.2 Inflammatory Chemokines and Cytokines in ADPKD*

Chemokines are responsible for infiltration, activation, and polarization of inflammatory cells and could regulate inflammatory cell behavior. One of the extensively studied chemokines in ADPKD is monocyte chemoattractant protein-1 (MCP-1, Ccl2), which binds to its cognate receptor CCR2. CCR2 belongs to the CC chemokine family of G-protein coupled receptors and typically expresses on the surface of T cells or monocytes (Li et al. 2008a). MCP1 was markedly increased in the cyst fluid of ADPKD patients and was associated with worsened renal function (Zheng et al. 2003). The increased expression of MCP-1 in rodent models of PKD paralleled the result observed in humans (Cowley et al. 2001). In vitro models, MCP-1 was produced by PKD1−/− tubule epithelial cells compared to the control cells (Song et al. 2017). Based on the increased MCP1 expression across different species, MCP-1

is proposed as a biomarker for ADPKD. Moreover, Cassini et al. (2018) found the upregulation of MCP-1 preceded macrophage infiltration in mouse polycystic kidney tissue. Macrophages accumulating around nascent cysts were pro-inflammatory and induced tubular cell injury and proliferation-independent cystic dilation (Cassini et al. 2018). One month later, macrophages switched to an alternative activation phenotype and further promoted cyst growth due to an additional threefold increase of tubular cell proliferative rates (Cassini et al. 2018). In PKD1-MCP1 double-knockout mice, there was a marked reduction in MCP-1 expression and macrophage numbers, resulting in slower cyst growth and improved renal function (Cassini et al. 2018). Treatment of PKD1−/− mice with Ccr2 inhibitor partially reproduced the improvement seen with MCP1 knockout (Cassini et al. 2018). Therefore, MCP-1 promoted macrophage accumulation and cyst growth via both proliferation-independent and -dependent mechanisms in ADPKD.

In addition to MCP-1, levels of TNF-α also increased in ADPKD cyst fluid with age and cyst severity (Li et al. 2008b). TNF-α is an immune cytokine which activates inflammatory signaling pathways and plays important roles in several biological processes. Furthermore, TNF-α plays a significant role in cyst formation where it interferes with processing and presentation of PC2 (Li et al. 2008b). Inhibition of TNF-α converting enzyme (TACE) led to a significant reduction in cyst volume (Dell et al. 2001). Taken together, TNF-α is a key contributor to cyst formation in ADPKD.

### *5.2.3 Complement System In ADPKD*

The complement system is activated by three pathways: the classical complement pathway, alternative complement pathway, and lectin pathway. Three pathways converge on C3, then C3 convertase cleaves C5 which activating C6–9. The alternative pathway accounts for about 80–90% of the total complement activation, even when initially triggered by the classical pathway or lectin pathway (Ricklin et al. 2010). The end of the complement activation is the enhancement of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, the promotion of inflammation, and the activation of membrane attack complex.

Growing evidence suggested that activation of the complement cascade contributed to ADPKD progression. Mrug et al. (2008) confirmed that innate immunity is involved in the PKD progression in mouse model, particularly abnormal C3 activation is a key element. Burtey et al. (Mrug et al. 2008) also confirmed the overexpression of nine complement–component genes (including C3) in Han: SPRD rat. The proteomic analysis of urine and cyst fluid from ADPKD patients with ESRD found 44 proteins including complement factors (Mason et al. 2009; Bakun et al. 2012. Mrug et al. 2014) further found that antigenic C3 was present in CLCs and that C3 activation fragments (iC3b) was present in renal cysts and urine from ADPKD patients, and iC3b might partly be responsible for cystogenic effects of M2 macrophages. Moreover, we found an excessive activation of alternative complement pathway in ADPKD progression (Su et al. 2014). Firstly, we screened the glycoproteome of urine

samples from ADPKD patients, revealed that levels of complement factor B (CFB) and C9 increased along with disease progression. CFB is the key factor in complement alternate pathway, which is cleaved by factor D into two fragments: Ba and Bb. Bb, a serine protease, then combines with complement factor 3b to generate the C3 or C5 convertase which initiate and sustain the activation of alternative pathway. Then, we evaluated the effect of the complement inhibitor rosmarinic acid (RMA) in Pkd1−/− mice and Han: SPRD Cy/+ rats. RMA-treated models showed significantly lower cystic index, better renal function, lower inflammatory cells, and reduced fibrosis. We further explored the mechanism of CFB overexpression and alternative complement pathway activation in ADPKD (Ming Wu 2016.). We observed that the overexpression of CFB was associated with increased JAK2/STAT1 activity and an enhanced expression of PC1 C-terminal tail (PC1-CTT). Moreover, STAT1 inhibition by fludarabine in renal epithelial cells suppressed Arg1 expression induced by PC1-CTT-CM, which suggested that PC1-CTT-induced macrophage activation into M2 phenotype might be mediated by STAT1 and CFB. In conclusion, the above findings prove that the complement activation, especially the alternative complement pathway takes part in ADPKD progression.

### *5.2.4 Pathways of Inflammation in ADPKD*

To date, NF-κB (Banzi et al. 2006; Qin et al. 2012) and JAK-STAT (Weimbs et al. 2013) pathways are the extensively studied pathways that correlate with inflammation in ADPKD. Pei et al. (Song et al. 2009) performed a global gene profiling in cysts from PKD1 mutant human kidneys. The analysis displayed a rich gene transcriptional profile for immune/inflammatory response including JAK-STAT and NF-κB signaling pathway.

Several studies have explored the mechanism of the NF-κB activation in ADPKD. NF-κB has been characterized as a key regulator of immune system for a long time and is responsible for the transcription of the genes encoding pro-inflammatory factors including TNF-α, IL1, CcL3, Ccl4, and MCP-1 (Hayden and Ghosh 2011, 2012; Pahl 1999). Qin et al. 2012 reported that c-Met and NF-κB-dependent overexpression of wnt signaling promoted cystogenesis in PKD. Park et al. (2010) reported that receptor of advanced glycation end product upregulated intracellular NF-κB signaling in PKD2 transgenic mice. Banzi et al. (2006) reported that PC1 activated a PKCα-mediated NK-κB signaling. Taken together, NF-κB is activated and induces inflammation responses in ADPKD.

The JAK-STAT pathway is the principal signaling mechanism for a wide array of cytokines and growth factors (Rawlings 2004), involving cell proliferation, differentiation, transcription, and immune response (John J. O'Shea 2013; Kaplan 2013). Anil Kumar Bhunia et al. (2002) first reported that PKD1 and PKD2 regulated activation of the JAK-STAT signaling pathway. The CTT of PC1 could undergo proteolytic cleavage (Qian et al. 2002; Wei et al. 2007) and nuclear translocation (Chauvet et al. 2004). In ADPKD kidneys, PC1 tail fragments are overexpressed, including both

30 kDa (a full-length) and 15 kDa fragments (a half-length). Weimbs et al. observed that cleaved PC1 tail interacted with STAT6 and P100, enhanced STAT6 activity (Low et al. 2006). They further reported that membrane-anchored PC1 activated STAT3, soluble CTT co-activated SATA1, 3, and 6, and STAT3 activated required JAK2 which interacted with PC1 tail (Talbot et al. 2011). In our laboratory, Ming Wu et al. (2016) showed that the PC1-CTT regulated CFB expression through JAK2/STAT1 pathway. We also showed that NF-κB acted as the downstream of PC1-CTT and might mediate PC1-CTT-induced CFB expression. The result suggested that targeting STAT1 and NF-κB might be a strategy to decrease inflammation in ADPKD.

## 5.3 ECM in ADPKD

The characteristic of tubule interstitial fibrosis is the accumulation of ECM proteins such as proteoglycan, collagen I, III, IV, V, elastin, fibronectin, and heparin sulfate proteoglycan (HSPG) (Wilson et al. 1996). ECM is a complex of proteins which fills the extracellular space in connective tissues. ECM mainly participates in cell supporting, cell adhesion, proliferation, differentiation, and fibrosis (Wilson et al. 1992). Abnormalities of ECM accumulation are found in human polycystic kidney tissue (pre-dialysis and ESRD) (Norman 2011; Wilson et al. 1992). ECM deposition and tissue remodeling are essential components of cyst progression (Wilson and Burrow 1999). The ADPKD-associated ECM abnormalities include disordered production, composition, and turnover (Wilson et al. 1996). Abnormalities most commonly appeared in cyst surrounding and interstitial basement membrane structures (Wilson et al. 1999).

Except the common factors which regulate the activity of pro-fibrotic pathways are same with the chronic kidney disease (CKD), recent animal studies indicated that polycystins might directly control ECM production (Liu et al. 2014). Upregulation of TGFβ, the major pro-fibrotic growth factor, was observed in PKD1 knock-out mice, and loss of PKD1 led to an increased responsiveness of cystic cells and fibroblasts to TGFβ (Hassane et al. 2010; Liu et al. 2014). Moreover, enhanced TGFβ pathway signaling and Smad2/3 nuclear localization were observed in ADPKD patients and rodent models (Hassane et al. 2010). Similarly, the loss of polycystin was associated with notochord collagen overexpression in zebrafish which was associated with fish body axis curvature defects (Mangos et al. 2010). Therefore, polycystin mutations play important roles in ADPKD-associated changes in ECM.

In addition, PKD-related changes in ECM were associated with other interstitial fibrosis factors like hepatocyte growth factor, epithelial growth factor (EGF), and fibroblast growth factor-1 (FGF1) (Du and Wilson 1995; Horie et al. 1994). Levels of these pro-fibrotic factors increased over time in ADPKD (Du and Wilson 1995). Pro-fibrotic factors might affect the pathobiology of early stages of ADPKD and the highest levels were found in near end-stage or end-stage ADPKD.

## 5.4 ECM Regulation and Turnover in ADPKD

When an imbalance of cytokines is generated in ADPKD, the abundance of pro-fibrotic factors such as TGFβ, PDGF, connective tissue growth factor, FGF2, and osteopontin are increased, whereas the abundance of anti-fibrotic factors such as bone morphogenic protein (BMP) 7 and hepatocyte growth factor are decreased (Song et al. 2017). More importantly, interstitial fibrosis is a consequence of both increased ECM production and inadequate matrix degradation which is another key regulator of fibrosis (Eddy 1996). Development of fibrosis in ADPKD and other fibrotic models depends on both the amount of produced ECM and the extent of matrix turnover during disease progression. Matrix metalloproteinases (MMPs) are responsible for degrading ECM proteins. Several classes of MMPs have been studied including collagenases such as MMP1, MMP8, gelatinases, metalloelastase, membrane-type MMPs, and others. Tissue inhibitors of metalloproteinases (TIMPs) inhibit MMPs (Catania et al. 2007). Consistent with the abnormal ECM change observed in polycystic kidney tissues, an imbalance renal expression of TIMPs and MMPs was found in kidneys of PKD (Norman 2011).

In kidneys, many types of MMPs and TIMPs are expressed, including MMP 2, 3, 9, 13, 14, 24, 25, 27, 28, and TIMP 1, 2, and 3 (Catania et al. 2007). Among them, MMP 1, 2, 9, 14, and TIMP1 are related to PKD (Catania et al. 2007). Increased MMP activity and collagen expression could stimulate the cyst formation in PKD. MMP2 is down-regulated in Han: SPRD rats, along with the upregulation of TIMP1 and TIMP2 (Schaefer et al. 1996). However, an overexpression of MMP2 was found in kidneys or tubules in ADPKD mice (e.g., Cys1cpk mice and PKD1−/− mice) (Hassane et al. 2010; Rankin et al. 1996). MMP-14 overexpression was found in kidneys of PKD1−/− mouse, Cys1cpk mice, and Han: SPRD rats (Grantham et al. 2011; Schieren et al. 2006). The suppression of MMP14 by batimastat was found to reduce cyst formation and kidney weight. Increased expressions of MMPs and TIMPs could induce remodeling and thickening of the cystic membrane, and the fibrosis was induced in CLCs (Song et al. 2017). Therefore, inhibitions of MMP 2, 14, and TIMP2 through sirolimus decreased the accumulation of ECM and alleviated PKD progression (Follonier Castella et al. 2010).

In humans, ADPKD was associated with increases of serum levels of MMP1, MMP9, and TIMP1 (Nakamura et al. 2000). There were increased levels of multiple MMPs, TIMPs (e.g., MMP2, MMP3, MMP9, TIMP1 and TIMP2), and plasminogen activator inhibitor 1 (PAI1) in both pre-dialysis and ESRD kidneys of ADPKD patients (Nakamura et al. 2000). The overexpression of PAI1 was reported in both human and mouse polycystic kidney tissues (Eddy 2009). It was believed that PAI1 was pro-fibrotic due to its ability to recruit macrophage and myofibroblasts to the tubulointerstitial area (Eddy 2009).

The functional consequences of these ECM turnover regulators are not fully understood in ADPKD. Consequences may include changes in several cellular functions (e.g., proliferation and differentiation) and immune regulation (breakdown collagen I into proline–glycine–proline (PGP) fragment) (Norman 2011; Snelgrove et al. 2010).

PGP is an important regulator of inflammatory neutrophil accumulation which is the key pathogenesis of chronic obstructive pulmonary disease (Snelgrove et al. 2010). MMP9 which participated in the generation of PGP was upregulated in ADPKD. PGP and other collagen fragments of ECM may play important immunoregulatory and modulating effects in polycystic kidney tissues.

Interactions between cells and ECM or its degradation products are mediated by matrix receptors such as integrins and syndecans (Geiger et al. 2001). Chemokine receptors often interact with ECM components at focal adhesion complexes which activate intracellular signaling to regulate major cellular processes (Ehrhardt et al. 2002). The complex interactions between ECM, receptors of ECM degradation fragments, signaling pathways, and ensuing transcriptional activation of specific genes form a unique microenvironment (Norman 2011). Studies demonstrated that several ECM receptors were increased in PKD patients, including integrins α2, β1, α8, β4, αv, syndecan-4, and integrin-associated focal adhesion kinase (Joly et al. 2003; Zeltner et al. 2008). ECM receptors (integrins α and β) may localize on primary cilia (McGlashan et al. 2006). Genetic disruption of integrin pathways could mitigate the renal cyst formation in mice (Desmouliere et al. 1993). Moreover, a hypomorphic mutation in laminin α5 gene could drive renal cyst formation (LeBleu et al. 2013). Therefore, the cell–ECM interactions may take part in PKD pathogenesis.

## 5.5 Cells in Regulation of ECM in ADPKD

### *5.5.1 Myofibroblasts*

Myofibroblasts are specialized cells which can exert contractile forces, mediate wound healing, and substantially contribute to the ECM expansion and development of renal interstitial fibrosis (Fig. 5.3) (Qi et al. 2006). The hallmark of myofibroblasts is the expression of cytoskeletal α smooth muscle actin (αSMA) (Norman 2011). αSMA-positive cells were found in kidneys of PKD1−/− mice and end-stage kidneys of Han:SPRD rats (Hassane et al. 2010). There were also αSMA expressing interstitial cells in focal areas of early-stage kidneys and in widespread areas of end-stage kidneys in ADPKD patients. The origin of myofibroblasts in polycystic kidney may differentiate from different precursors such as resident interstitial fibroblasts (LeBleu et al. 2013). In a model of renal fibrosis, most myofibroblasts were derived through the proliferation of resident fibroblasts, although bone-marrow-derived fibrocytes also contributed about 35% of total myofibroblasts in the kidney (LeBleu et al. 2013). Myofibroblast transformation could be regulated by TGFβ or by the alteration of calcium flux in PKD (Desmouliere et al. 1993; Follonier Castella et al. 2010). Myofibroblasts also could differentiate from infiltrating inflammatory cells (Wada et al. 2011).

After appropriate stimulation, fibroblasts may differentiate into myofibroblasts. The stimulation may be enhanced in ADPKD in response to increased ECM-

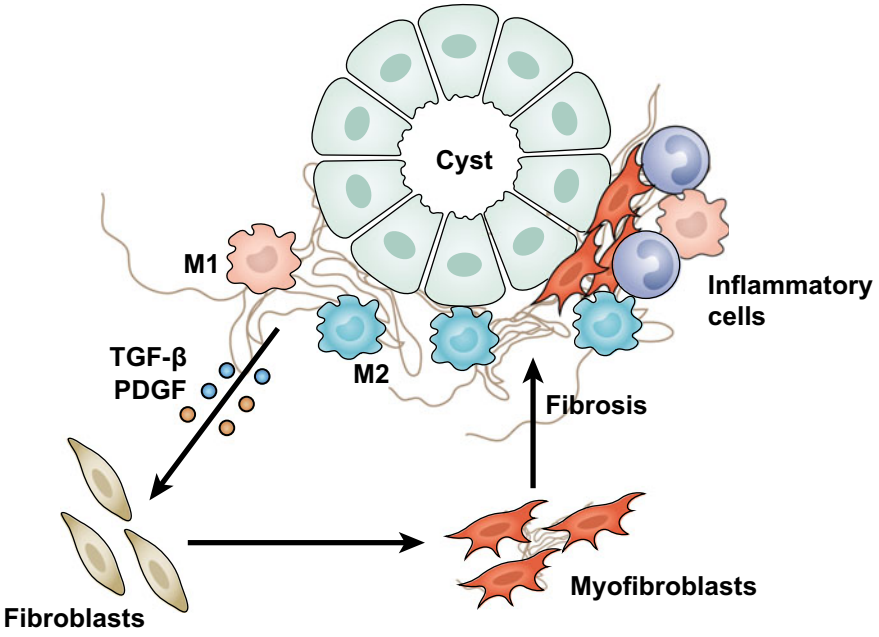


**Fig. 5.3** Cells and pathways in the regulation of fibrosis in ADPKD. The persistent increase in inflammatory cells including macrophages leads to enhanced secretion of pro-inflammatory and pro-fibrotic cytokines which causes the transition of fibroblasts and fibrocytes to a myofibroblast phenotype. These myofibroblasts produce large amounts of ECM proteins leading to the deposition of collagen into ECM and fibrosis in ADPKD

promoting factors such as TGFβ, FGF1, platelet-derived growth factor (PDGF), and insulin-like growth factors (IGF) I and II (Kuo et al. 1997). These changes also included increased secretion of MMP2 and heat shock protein 47. Similar changes of TGFβ pathway activation and the proliferative response were observed in embryonic fibroblasts in PKD1−/− mice (Nishio et al. 2005). In addition, fibroblast differentiation to myofibroblasts could be modulated by macrophages that secrete growth factors including FGF2, PDGF, galectin 3, and IGF binding protein 5 (Huen and Cantley 2015).

### *5.5.2 Fibrocytes*

Fibrocyte is another ECM producing cell. Fibrocytes differentiate from peripheral blood leukocytes and express both hematopoietic and stromal cell markers, as well as several chemokine receptors (Wada et al. 2011). The differentiation of fibrocytes is enhanced by cytokines associated with repair and pro-fibrogenic Th2-type immune response and is inhibited by pro-inflammatory Th1-type cytokines (Niedermeier

et al. 2009). Because the speed of PKD progression was associated with the Th2-type immune response, fibrocyte differentiation may be enhanced in cystic kidneys and contribute to ECM abnormalities in ADPKD (Qi et al. 2006).

### *5.5.3 Inflammatory Cells*

Inflammatory cells are involved in fibrosis progression of ADPKD. Inflammatory cells serve as potent producers of pro-fibrotic, pro-inflammatory, and pro-mitotic cytokines. Understanding the involvement of inflammatory cells and related signaling pathways in cyst fibrosis will provide innovative insights into the mechanism of PKD progression.

The most studied inflammatory cell associated with fibrosis in ADPKD is the macrophage. The macrophage accumulation accelerates the proliferation of CLCs and increases cytokines which cause fibrosis in ADPKD (Vernon et al. 2010). Macrophages include a heterogeneous group of cell types which differ from origin and activation (Anders and Ryu 2011). The involvement of macrophages in promoting the accumulation and degradation of ECM was well established. Macrophages secrete cytokines such as IL-10, MCP1, TNF-α, TGF-β, PDGF, or Arg1, which induce myofibroblast activation and ECM production (Anders and Ryu 2011). Then, myofibroblasts produce lots of ECM proteins which lead to fibrosis in polycystic kidneys. M1 macrophages produce TNF-α and encourage inflammation. M2 macrophage stimulates the tubular cell proliferation and fibrosis formation. In normal condition or ADPKD, renal epithelial cells could promote the differentiation of naïve macrophages into M2 macrophages (Vernon et al. 2010). Recently, M2 macrophages associated with Th2 cytokine-driven responses were found to promote renal tissue repair and fibrosis. M2 macrophages were also associated with ADPKD progression (Mrug et al. 2008). CD11b was used as the identification of the pro-fibrotic bone-marrow-derived macrophage (Lin et al. 2009). However, some macrophage types have fibrosis attenuating effects in ADPKD. Those macrophages produced several matrix-degrading proteases including MMP1, 2, 8, 9, and 13 (Semedo et al. 2010). In a UUO model, adoptive transfer of bone-marrow-derived macrophages into leukocyte-depleted mice could significantly attenuate fibrosis (Qi et al. 2006). Together, these data suggest that different macrophage subtypes could promote or regress fibrosis. In addition to macrophages, renal fibrosis and ECM abnormalities may be enhanced by lymphocytes, CD11c dendritic cells, and mast cells.

## 5.6 Epithelial Mesenchymal Transition

Renal vascular and tubular epithelial cells or macrophages can transit to a myofibroblast phenotype through epithelial mesenchymal transition (EMT). TGFβ is recognized as the main EMT inducer. In PCK rats, an orthologous model of human

PKD, e-cadherin and β-catenin in cystic tubules were attenuated and localized to lateral areas of cell–cell contact (Mun and Park 2016). Epithelial cells in cysts of PCK rats acquired mesenchymal features through EMT in response to cyst enlargement and participated in progressive renal fibrosis. However, EMT was found to make negligible contributions to the pathogenesis of renal cysts of ADPKD (Mun and Park 2016). Although EMT plays an important role in the formation of kidney myofibroblasts, the extent of EMT and its importance for the fibrosis in ADPKD patients is unknown.

## 5.7 Prognostic Value of ECM Abnormality in ADPKD

Recently, abnormal expression of collagen I and III derived fragments were identified in the urine of young pre-dialysis patients with ADPKD (Kistler et al. 2009). ECM remodeling may be an attractive predictive biomarker and a therapeutic target for development. A follow-up study based on the analyses of urinary collagen fragments provided further support for the hypothesis (Kistler et al. 2013). The study found that urinary proteomic score (mostly urinary collagen fragments) predicted ADPKD severity significantly (Kistler et al. 2013).

## 5.8 Fibrotic Signaling Pathways

Several intracellular signaling pathways in fibrosis are activated in ADPKD.

### *5.8.1 TGFβ-SMAD Signaling Pathway*

TGFβ is highly expressed in CLCs of human and rodent models of PKD (Hassane et al. 2010). The TGFβ pathway is usually related to fibrosis, proliferation, cell—cell interaction, apoptosis, and cell differentiation (Sureshbabu et al. 2016). TGFβ is secreted by macrophages, lymphocytes, and dendritic cells. When TGFβ binds to its receptors, TGFβ receptor types I and II will assembly and activate receptor I. Then, the activated receptor I phosphorylates receptor-regulated SMAD which binds to the common-mediator SMAD (Leonhard et al. 2016). The SMAD complex then translocates to the nucleus and activates gene transcription. Increased TGFβ expression and SMAD signaling were found to correlate with the late-stage fibrosis of ADPKD and play an important role in cyst fibrosis and the disease progression rather than cyst initiation (Norman 2011). The expression of TGFR1 and 2 was found to be elevated in the PKD1−/− mouse model (Chen et al. 2008). Moreover, the inhibition of TGFβ could decrease cyst formation and ADPKD progression. However,

TGFβ2 was found to alleviate ADPKD progression and cystogenesis by controlling the synthesis of ECM proteins and cell adhesion (Elberg et al. 2012).

Activin A is a cytokine belonging to the TGFβ family of growth factors. During kidney development, activin A is produced by ureteric bud (UB) and negatively regulates UB branching (Yamashita et al. 2004). Furthermore, activin A is involved in kidney regeneration following injury, suggesting an important role for activin A during kidney formation or regeneration. The inhibition of activin A signaling could slow the progression of PKD (Leonhard et al. 2016). In addition, the level of activin A increased in PKD1−/− mouse model and was associated with conditions wherein dysfunction of the cilia or polycystins caused rapid cyst formation (Yamashita et al. 2004). These studies indicated that activin A was a critical cytokine in cyst progression and ESRD since it was involved in epithelial regeneration and was capable of inducing ECM gene expression in kidney (Yamashita et al. 2004).

### *5.8.2 Wnt Signaling*

Because β-catenin regulates the EMT process, Wnt signaling pathways are closely connected with fibrosis. There are three types of Wnt signaling pathways including the canonical Wnt pathway, the non-canonical Wnt/Ca2 + pathway, and the non-canonical planar cell polarity pathway. Wnt signaling regulates gene transcription, proliferation, cytoskeletal structure, and cell migration (Komiya and Habas 2008). When Wnt is absent, complexes that contain disheveled, glycogen synthase kinase-3β, axin, and adenomatous polyposis coli degrade β-catenin in the canonical Wnt pathway. When Wnt is present, the complex is inhibited, then β-catenin accumulates and functions as the transcription factor. A transgenic mouse model that constitutively expressed β-catenin developed PKD (Qi et al. 2006). The activity of Wnt signaling was increased in CLCs of patients with ADPKD (Mun and Park 2016). The expression of Wnt4 related to EMT increased in jck mice (Stark et al. 1994). In Gpr48−/− PKD mice, renal fibrosis was found to accompany the Wnt signaling pathway activation (Dang et al. 2014). Moreover, the Wnt signaling regulated primary cilia formation. Genetic knockout of ciliary proteins Bbs1 and Kif3a showed an activation of Wnt signaling in transgenic mice compared with normal mice (Corbit et al. 2008). Likewise, the upregulation of Wnt signaling increased the expression of fibronectin. Together, the overactivation of Wnt signaling results in an increased frequency of EMT and lead to fibrosis in ADPKD.

### *5.8.3 Periostin–Integrin-Linked Kinase Signaling*

Periostin is a secreted protein which binds to the ECM components including collagen I and fibronectin and has been implicated in collagen fibrillogenesis (Wallace et al. 2014). Periostin was markedly overexpressed and could promote cyst growth and

interstitial fibrosis in PKD mice (Wallace et al. 2014). Several integrins including α and β also were aberrantly expressed in CLCs. Integrin-linked kinase (ILK), which is stimulated by periostin, directly binds to β integrins and links the ECM to the actin cytoskeleton. Periostin-ILK signaling played a role in cytoskeleton reorganization by recruiting regulatory proteins such as parvin, paxillin, and kindlin2 (Raman et al. 2017). Raman et al. (Raman et al. 2017) found that knockdown of ILK and its downstream signaling strikingly reduced PKD fibrosis and extended the life of PKD mice.

## 5.9 Anti-fibrotic Therapies in ADPKD

Slowing the cyst expansion and development of fibrosis is very important to prolonging life span and improving palliative care of patients with ADPKD. However, the development of effective anti-fibrotic treatments in ADPKD patients is limited. Identifying the key molecular mechanism of fibrosis and how it contributes to ESRD will provide novel targets for anti-fibrotic therapies (Vilayur and Harris 2009). For example, targeting of αSMA-positive cells for anti-fibrotic therapy to help reduce scarring and retain renal function may be an attractive idea in the future (Song et al. 2017). B-type natriuretic peptide overexpression was found to ameliorate renal fibrocystic disease through the guanylyl cyclase A-cGMP axis in a rat model of ADPKD (Holditch et al. 2017). We previously found that rosiglitazone, a peroxisome-proliferator-activated receptor-γ agonist, was able to down-regulate the abnormally activated β-catenin signaling pathway and delay the progression of fibrosis in Han: SPRD rats (Dai et al. 2010). In addition, targeting other fibrotic factors may alter the pathobiology of cyst formation and ADPKD progression. For example, overexpression of BMP receptor activin receptor like kinase 3 or BMP7 knockout, could trigger renal cysts formation in mice through SMAD/WNT signaling (Hu et al. 2003). BMP7 treatment was found to attenuate the renal cystic disease progression in Nek8 jck mouse model, and soluble activin-type IIB receptor treatment could effectively block cyst formation in a mouse PKD model (Leonhard et al. 2016). Similarly, EGF is another important regulator of cystic epithelial cell proliferation through EGF pathway which is explored for therapeutic development of ADPKD (Du and Wilson 1995). Better understandings of mechanisms underlying the initiation and progression of fibrosis in ADPKD are urgently needed.

## 5.10 Conclusion

The fibrosis is increased in the late-stage and end-stage ADPKD. Inflammation can initiate fibrosis, causing thickening of tubular membrane and remodeling of the interstitium. However, inflammation and fibrosis alone cannot generate ADPKD, which also requires CLC proliferation. Following an increase in cystic cell proliferation,

fibrotic cells and pro-inflammatory cytokines are elevated and then lead to the development of inflammation, fibrosis, and proliferation. Macrophage and its secreted cytokines accumulated in cystic fluids and urine of PKD. TGFβ, MMPs, and TIMPs could trigger fibrosis in ADPKD. MMPs and TIMPs could induce the accumulation of fibroblasts and collagen. The inhibition of cytokines involved in fibrosis could be a therapeutic strategy for ADPKD.

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