Chapter 14

Role of Inflammation in Polycystic Kidney Disease

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Abstract

Polycystic kidney disease (PKD) is a genetic disorder that is characterized by progressive growth of multiple cysts in the kidneys. Two forms of the disease exist, autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ADPKD is the most common form of genetic disorder of the kidney. In the United States about 600,000 people have PKD. This disease eventually leads to end stage kidney disease (ESKD) which may take as long as three decades to develop and requires renal replacement therapy. PKD is the fourth largest cause of kidney failure. Interstitial inflammation is a common component of chronic kidney disease (CKD) and, it is a better prognostic marker, than glomerular

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health, for progression of the disease or kidney function. PKD is no exception. Markers of inflammation are present much earlier than detectable cyst growth and correlate with the disease progression. While in other kidney diseases interstitial inflammation is mostly associated with interstitial fibrosis, in PKD inflammation is also linked to cyst progression. Inflammatory cells such as macrophages have been reported in both human and experimental animal models of PKD, with the degree of macrophage infiltrate associated with disease progression in humans. In animal models of PKD, macrophages have been associated with cyst growth and deteriorating renal function. What may differentiate PKD from the rest of the CKD is that experimental evidence suggests a direct role of PKD genes in regulating expression of some of the pro-inflammatory chemoattractants such as monocyte chemoattractant protein-1 (MCP-1) and other cytokines. Indeed, increased urinary levels of MCP-1 correlate with the progression of disease in humans. This chapter will highlight some of the work that provides evidence for the role of inflammation in disease progression in PKD.

Key Words: Chemokines; Cytokines; Inflammation; Macrophages

Introduction

Polycystic kidney disease (PKD) is one of the most common genetically inherited causes of chronic kidney disease (CKD) that leads to end stage kidney disease (ESKD) requiring renal replacement therapy (1). PKD may be inherited as either an autosomal dominant (ADPKD) or autosomal recessive trait (ARPKD). ADPKD is the most common form of PKD and is estimated to account for 7-10% of ESKD patients (1-4). ADPKD is caused by inherited or *de novo* mutations in *PKD1* and/or *PKD2* genes that encode ciliary proteins, polycystin 1 (PC1) and polycystin 2 (PC2) respectively (5, 6). The majority of cases are attributed to mutations in the *PKD1* gene (~ 85%) (7, 8). PKD exhibits tubular dilatation and bilateral fluid-filled cyst formation (4, 9, 10). Cysts in ADPKD develop slowly over a period of decades until ~ 60% of the parenchyma is destroyed after which renal function starts deteriorating rapidly, usually beyond the fifth decade of life (11) (Figure 1). It is estimated that cysts originate from not more than 1% of the total nephrons (12). Cysts form in cortex and medulla, although the medullary cysts may impact a larger number of nephrons. Since a single collecting duct drains ~ 2,800 tubules (13), it has been proposed that a cyst in a single collecting duct (in the papilla) could theoretically impact/impede 2,800 tubules (that may otherwise be normal) and negate their contribution to concentrating urine (14). Similarly, it has been further proposed that a cyst of ~ 400 μm in diameter could potentially block at least 32 adjacent tubules (explained in detail and illustrated in (14). In addition, these

expanding cysts (like fluid-filled balls) compress the surrounding tubuli and microvasculature, impeding both urine and blood flow. This leads to focal intrarenal hypoxia and cascades into a chronic inflammatory response causing further damage that is independent of the effects of the underlying genetic mutations. This is one mechanism whereby a small number of affected tubuli (~ 1%) could cause such extensive and progressive damage.

During the last two decades enormous understanding has been gained about molecular and cellular mechanisms that lead to cyst formation and expansion (8). Experimental evidence implicates abnormal / dysfunctional proteins associated with PKD1/2, cyst expansion causing anatomic distortion of the kidneys, factors present within the cysts, dedifferentiation of tubular epithelial cells (before the cysts separate from the tubule) and a multitude of signaling cascades (1, 11). However, another component that may contribute to the progression of PKD is the chronic interstitial inflammation. This chapter will bring to the fore our current understanding of what role, if any, inflammation might play in overall progression of PKD.



Figure 1. Gross specimen showing massively enlarged kidney with multiple cysts. Picture courtesy of Dr. Moeckel, Department of Pathology, Yale School of Medicine, New Haven, CT – USA.

Brief clinical description

Bilateral kidney cysts that at later stages lead to impaired function characterize ADPKD, which occurs with equal frequency among males and females. The disease generally manifests after the third or fourth decade and is often diagnosed upon a sudden episode of hematuria, renal pain or accidental finding on radiological examination, or presentation with hypertension (11). Hypertension precedes any significant decline in glomerular filtration rate (GFR) and may already be present in the third decade (15). Thus, in a majority of patients renal dysfunction remains undiscovered until GFR declines to abnormal levels. Typically GFR may not decline in PKD until the total kidney volume has exceeded five times that of a normal kidney volume and the decline thereafter averages 4-7 $ml.min^{-1}.yr^{-1}$ (16, 17) (18). The disease may be accompanied by several extrarenal manifestations that include liver and pancreatic cysts, cardiac valve defect, pericardial effusion, brain aneurysm (~8% of patients), abdominal wall hernia and hypertension (16, 19-21).

Initiation of cyst formation

The disease progression in ADPKD may be thought to have two parts – one of cyst initiation and the second of progression or expansion accompanied by declining renal function. The fundamental pathophysiology stems from the loss of PC1 and/or PC2 function due to the mutations in their respective genes. PC1 and PC2 have been shown to function in a complex as a transient receptor potential channel regulating intracellular calcium homeostasis either at the cilia or endoplasmic reticulum (ER) (22-25). In the primary cilium, the PC1/PC2 complex is believed to act as a sensor for inducing the influx of extracellular calcium following flow-mediated shear stress (26-28). In the ER however, it functions as a calcium release channel (22, 23). Experimental evidence suggests that following the loss or dose reduction of PC1/PC2 proteins there is an increase in epidermal growth factor (EGF) and cAMP-dependent tubular epithelial cell proliferation, tubular cell apoptosis (in very early stages), abnormal fluid secretion, loss of apico-basal polarity and changes in the extracellular matrix (29-32). The role of cAMP signaling in ADPKD has been studied extensively and has led to approval of the first drug, Tolvaptan (a vasopressin receptor antagonist) in Canada and Europe, discussed in detail elsewhere (18, 33-35). It is awaiting approval in the United States. A recent study in a hypomorphic mouse model of PKD1 demonstrated that adding a somatostatin receptor inhibitor, Pasireotide, along with Tolvaptan, had an additive effect on reducing cyst burden as well as fibrosis (36). Both, Tolvaptan and Pasireotide target adenylyl cyclase 6, the predominant form of adenylyl cyclase in the collecting duct.

Although all cells of the body carry the PKD mutations, only a small number of tubules give rise to cysts (11). This phenomenon is attributed to occurrence of a second somatic hit in the normal copy of the gene which then leads to loss of function in a small subset of tubular epithelial cells and the cyst formation gets initiated (37-40). ESKD occurs at an earlier age (54 years) in patients with a PKD1 mutations than in those with PKD2 mutations (70 years) (41).

This is thought to be due to a greater number of cysts with PKD1 mutations as compared to PKD2 mutations. The rate of cyst growth is not thought to be different. A recent study has shed new light on the function of polycystins, cilia and how their interplay might regulate cyst formation. The study demonstrates that polycystin acts as suppressor while cilia provide a positive stimuli for cystogenesis suggesting that this could be yet another mechanism for cyst growth independent of ERK, cAMP or mammalian target of rapamycin (mTOR) pathways (42).

Regardless of the signaling mechanisms, after acquiring the second hit, monoclonal expansion of the affected cells initiates the cyst development. Persistent proliferation of these cells leads to radial expansion of the tubule eventually taking a shape of a sac-like bud (illustrated in (14)). It is interesting to note that normal tubular epithelial cells such as inner medullary collecting duct cells have a propensity to assemble into a lumen-containing tubule-like structure, when suspended in a 3D collagen/matrigel mixture (43). In contrast, tubular cells lacking PC1 or PC2 by default form cyst-like structures suggesting a phenotypic switch due to the lack of polycystins (44, 45). Cysts eventually separate from the tubule as independent 3D structures and create obstruction in the parenchyma by compressing adjacent tubules and vasculature thereby creating a secondary phenomenon resembling obstructive nephropathy. Indeed similarities have been drawn between ADPKD and the rodent unilateral ureteral obstruction (UUO) model of nephropathy (14). Both induce a similar array of chemokines and cytokines (14). However, in humans the cysts grow slowly at least for the first three or four decades. Despite slow cell proliferation, the kidney volume in ADPKD progressively increases at a rate of 5-6% annually suggesting that cell proliferation alone may not account for the expansion of the renal volume (16, 46). The phenotypic changes in the mutant cells paired with the distortion of the otherwise normal tubules and vessels, sets in motion an inflammatory response that has the hallmark of an acute reparative response but ends up being chronic and pathological leading to fibrosis. Indeed, very early on, researchers had noted significant changes in matrix and cell dedifferentiation in histopathology analysis of kidney tissue from ADPKD patients (47, 48). Inflammation in chronic kidney disease (CKD) has been known for over a decade now. Its potential contribution to the progression of ADPKD has been in focus only recently.

Inflammation in CKD

Inflammation is a protective physiological response that is initiated to neutralize the initial cause of cell or tissue injury (such as a pathogen) and to clean off the by-product of the injury, necrotic or apoptotic cells or tissues (49). However, an inflammatory response must be tightly regulated to avoid any damaging effects that could lead to mortality (49). Several studies have demonstrated the importance of inflammation in CKD (50-52) and have indicated that persistent inflammation also increases risk for cardiovascular disease (CVD)-dependent mortality in ESKD patients (53-55). CVD is also responsible for ~ 80% deaths in ADPKD (56, 57) highlighting a potential detrimental role of inflammation in ADPKD.

There are two main types of inflammation processes, active and chronic. Active or acute inflammation is triggered within hours/days. Histologically, it is defined by the presence of neutrophils that have migrated from the bone marrow to the site of injury. It also includes eosinophils and basophils (mast cells), the latter typically seen in response to an allergy. In contrast, chronic inflammation occurs within weeks/months. Histologically, it is represented by the presence of mononuclear cells – lymphocytes and macrophages (differentiating from circulating monocytes). However, active inflammation, tissue repair and destruction may co-exist with chronic inflammation, as is the case in CKD.

Inflammation in PKD

Subclinical inflammation has been linked with progression of CKDs (52, 58). Similar evidence in the progression of ADPKD is scarce. Generally speaking, PKD is not an inflammatory disorder. However, evidence is gradually accumulating to indicate onset of inflammation very early in the course of the disease. The presence of an inflammatory component in humans with PKD, as well as rodent models of the disease, has been reported in a few studies. For example, interleukin (IL)-1β, tumor necrosis factor-α (TNF-α and IL-2 (proinflammatory cytokines) were observed in cyst fluid of human PKD kidneys (59-61). Monocyte chemoattractant protein-1 (MCP-1) was detected in urine of ADPKD patients and urinary MCP-1 levels correlated positively with the progression of ADPKD in humans (61). Similarly, increased *Mcp-1* expression was reported in Han:SPRD rats, a nonorthologous model of ADPKD (62). More recently, genes involved in the innate immune response were found to be the most significantly upregulated genes in severely cystic *cpk* mice, a nonorthologous mouse model of ARPKD (63). These findings were further validated by Zhou and co-workers who found significantly higher expression of the markers of monocytes and macrophages in severely cystic *cpk* mouse kidneys. Specifically, they found CD14, a marker of alternatively-activated macrophages, to be highly upregulated and activated (64). CD14 is a pattern recognition receptor that engages with Toll-like receptors (TLRs) to activate innate immune response. In yet another recent study, a systems biology approach revealed a rich profile of genes associated with inflammatory responses in cystic human tissues from five PKD1 mutant kidneys (65). Soon after, in a cross-sectional study, Menon and co-workers reported that hypertensive ADPKD patients with eGFR of 25 to 60 ml/min had higher levels of inflammatory markers such as C-reactive protein (CRP) and IL-6 compared to healthy controls, normotensive ADPKD with eGFR >60 and hypertensive ADPKD with eGFR of >60 (66). Although the study size was relatively small, the data nonetheless indicate the presence of inflammation early in ADPKD even when the renal function is preserved. Moreover, the authors also found a linear increase in these inflammatory markers with declining kidney function, suggesting a causal relationship of inflammation to the disease progression. In contrast, markers of oxidative stress, while high across ADPKD with varied renal function, did not change with the progression of disease. Kocyigit and co-workers examined a temporal relationship between ADPKD, hypertension and the loss of renal function in fifty patients with ADPKD who did not yet have hypertension (67).

The results indicated increased pulse wave velocity and arterial stiffness occurred even before detection of hypertension and reduced eGFR. The same group recently determined that pentraxin-3 (PTX-3) is a better marker of inflammation and endothelial dysfunction than CRP. In ADPKD patients, PTX-3 had already increased even before any changes in their blood pressure or change in eGFR. PTX-3 correlated positively with proteinuria and uric acid, once again suggesting that inflammation occurs much earlier and may contribute significantly to the progression of disease (67). However, these vascular abnormalities are signs of systemic subclinical inflammation (68) suggesting that inflammation (vascular) predates any measureable renal deterioration. Thus, gradually, evidence is accumulating that suggests a potentially significant role of inflammation in the progression of ADPKD.

How might inflammation contribute to disease progression in ADPKD?

When in 1970, it was reported that lymphocytes from some glomerulonephritis patients showed *in vitro* reactivity against glomerular basement membrane (69), this led to an editorial with the title: "what are sensitized cells doing in glomerulonephritis?" (70). This occurred because the existing view was that humoral immunity was responsible for immune-mediated kidney disease. The immune response can be divided into two general types: innate and adaptive immune responses. The innate immune system consists of cells and proteins that are already present and can be mobilized promptly as a first line of defense to fight pathogens at the site of infection or tissue injury. The innate immune system is comprised of: 1) epithelial cells; 2) phagocytic leukocytes; 3) dendritic cells; 4) natural killer (NK) T cells; and 5) circulating plasma proteins. The adaptive immune system is activated against pathogens that evade the first line of defense. The adaptive immune system is comprised of: 1) a humoral response mediated by B-lymphocytes via antibodies; and 2) cell-mediated by T-lymphocytes. The experimental evidence suggests that accumulation of phagocytic leukocytes and lymphocytes is a constant feature of chronic kidney damage, particularly in the areas of active tubulointerstitial injury and correlates with the severity of renal failure (71-73).

Mononuclear phagocytes in kidney injury and disease

Acute kidney injury (AKI) that is associated with long-term risk for CKD evokes a robust innate immune response. The innate immune response to tissue injury leads to local upregulation of chemokines that facilitate recruitment of neutrophils and naïve monocytes to the site of injury. The microenvironment that is defined by the local milieu at the site of inflammation then promotes maturation of these monocytes to macrophages. Macrophages in turn respond by secreting factors that will either enhance or dampen or simply modulate the inflammation. Several rodent studies indicate that, following recruitment to the site of injury, macrophages are initially activated to a pro-inflammatory state (M1 phenotype) by factors derived from either pathogens, pathogen-associated molecular patterns (PAMPs) or from injured cells themselves called danger-associated molecular patterns (DAMPs). Both

PAMPs and DAMPs are recognized by pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) and activate signaling via nuclear factor kappa B (NF-κB) inducing pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α (74). One major role of M1 type macrophages is to clear out the apoptotic cells or necrotic debris and prep the injured area for repair. Tissue repair is carried out by alternatively activated anti-inflammatory M2 type macrophages and these can be further categorized into wound healing or immunoregulatory subtypes (discussed in detail in (75)). However, macrophages are highly plastic and can trans-differentiate in response to the tissue microenvironment (76-78). In a mouse ischemia-reperfusion model of AKI, Lee and co-workers depleted macrophages in the initial phase of renal injury and determined that M1 type macrophages contribute to tubular injury. Conversely, when macrophages were depleted during the repair phase, the tissue injury worsened. If M2 macrophages were injected in the initial injury phase, lesser tubular injury was observed (79-81). Similarly, studies in the CCR2 (receptor for MCP-1, the major chemoattractants for circulating monocytes) knockout mice determined that CCR2-dependent macrophage recruitment was critical for promoting tubular injury (80, 81). Lee and co-workers made an important discovery that M2-macrophages provided reparative support by promoting proliferation of the surviving tubular cells (79). In contrast, interferon gamma activated macrophages (M1) did not induce tubular cell proliferation. What is also important to note that when M1 activated macrophages were injected into injured mice, these macrophages switched to M2 type. In-vitro studies indicate that factors secreted by tubular cells can induce macrophages to M2 reparative sub-type (79). The observation that M2 macrophages induce tubular cell proliferation provided the rationale for the hypothesis that macrophages in PKD could promote cyst expansion by inducing tubular cell proliferation (discussed below).

Macrophages accumulate in ADPKD kidneys and promote cyst growth

Macrophage-induced proliferation of cells had been proposed almost three decades ago when it was discovered that activated macrophages could induce proliferation in vascular endothelial cells, *in vitro* (82). As mentioned above, macrophages home to injured tubular segments of an ischemically-injured rodent kidney in response to factors like MCP-1, IL-6 and stromal cell-derived factor-1 (SDF-1) secreted by injured tubular or endothelial cells (83). Mononuclear cell infiltrates are present in human PKD kidneys (84, 85) likely due to upregulated MCP-1 (59, 61). Abundance of genes associated with the innate immune response was found in a model of recessive PKD. Indeed most of the markers were related to alternatively-activated macrophages (63). Using an orthologous model of PKD1, C57Bl6 *Pkd1*$^{fl/fl}$*;Pkhd1-Cre* mice, we provided the first evidence that macrophages could augment cyst growth. In these mice, the cysts start developing from postnatal day 10 and the mice start dying because of renal failure, due to massive cyst growth, by postnatal day 24. We first discovered that, compared to *Pkd1*$^{fl/+}$*;Pkhd1-Cre* mice, the *Pkd1* null mice harbored ~ ten-fold greater number of F4/80^{+}CD45^{+}CD11c^{-} macrophages, the majority of which lay in close apposition to cyst-lining epithelial cells. A similar observation was made in *Pkd2*$^{WS25/-}$ mice (a model of PKD2). Using quantitative PCR we then determined that PC1 null tubular cells express seven-fold greater amounts of *Mcp1* and five-fold greater chemokine (C-X-C)

ligand-16 (*Cxcl16*). Thus, a necessary chemotactic gradient exists to attract circulating monocytes and lymphocytes to a PKD kidney. Finally, depletion of macrophages by administering liposomal clodronate, that once taken up by phagocytic macrophages induces apoptosis, to the new born *Pkd1$^{fl/fl}$;Pkhd1-Cre* mice retarded cyst growth, led to decreased cystic index and improved renal function (blood urea nitrogen values) as compared to vehicle-treated *Pkd1$^{fl/fl}$;Pkhd1-Cre* mice. More importantly, depletion of macrophages correlated with reduced proliferation of cyst-lining cells without affecting the rate of apoptosis. Also, interestingly, the majority of these macrophages were Ly6C^{low}, consistent with the alternatively-activated macrophage phenotype (86). This study therefore provided a proof of concept, that in ADPKD, inflammatory cells such as macrophages can actively participate in cyst growth or expansion by activating proliferation of cyst-lining epithelial cells. Swenson-Fields and co-workers validated our findings in *cpk* mice model of ARPKD (87). Additionally, they demonstrated the presence of M2 macrophages in kidneys of patients with either ADPKD or ARPKD. Furthermore, they went on to demonstrate that renal tubular cells from ADPKD cysts or noncystic kidneys promote differentiation of naïve macrophages to the M2-like phenotype, in culture. Similar to our study, by depleting macrophages in *cpk* mice, they were able to demonstrate that these innate immune cells promote proliferation of cyst-lining cells (87). Together, these two studies provide biological relevance to previous reports of a strong correlation between expression of the monocyte/macrophage marker CD14 and the rate of cystic progression in *cpk* mice. CD14 expression also correlated positively with an increase in kidney volume that reflects cyst expansion (64).

Along similar lines, a more recent study has determined that macrophage migration inhibitory factor (MIF) promotes cyst growth in *Pkd1$^{fl/fl}$;Ksp-Cre* and *Pkd1$^{fl/fl}$;Pkhd1-Cre* mice, murine orthologous models of ADPKD (88). MIF is expressed by activated T lymphocytes, macrophages/monocytes, endothelial cells, epithelial cells, cells of anterior pituitary, smooth muscle cells and the synovial fibroblasts, suggesting that perhaps it may play multiple context and/or cell-dependent roles (89-94). Indeed, MIF regulates multiple cellular activities by transcriptionally regulating expression of several inflammation-related gene products such as SRC, ERK, mTOR, AMPK, AKT, p53, TNF-α and MCP-1 (95-102), most of which are also activated in PKD. The authors demonstrated that renal tubular cells lacking *Pkd1* had increased expression of MIF as was also the case in ADPKD kidneys and the cyst-lining epithelia of these kidneys. Treating these mutant mice with a small molecule inhibitor of MIF, isoxazoline (ISO-1), delayed cyst growth that correlated significantly with decreased proliferation of cyst-lining cells and improved renal function. In contrast to our data (after macrophage depletion), they observed increased apoptosis as well. The treated mice had remarkably better parenchyma. These data were further validated in the *Pkd1$^{fl/fl}$;Ksp1-Cre* mice lacking MIF wherein fewer macrophages were observed in interstitial and pericystic areas of the double mutant kidneys. The authors determined that MIF is normally secreted by kidney tubular epithelial cells and this is further enhanced by the loss of *Pkd1*. MIF also induced MCP-1 suggesting that MIF could be upstream of the MCP-1 axis and could therefore regulate trafficking of mononuclear cells into ADPKD kidneys. MIF was also detected in the cyst fluids and urine of ADPKD patients. They further determined that MIF could directly induce cell proliferation by activating ERK via Src kinase and

mTOR pathways by controlling phosphorylation of S6, a substrate of mTOR complex-I. In addition, by activating the p53 pathway, MIF seems to enhance apoptosis in *Pkd1* mutant cells but not in the wild type (WT) cells, which is very important, if it were ever to translate into a therapy (88). Thus, MIF seems to give a bigger "bang for the buck" by affecting multiple aspects of cyst growth and could be an attractive therapeutic target. However, one must be cautious and make sure that inhibition of MIF does not induce apoptosis in normal healthy cells after long-term administration. Given that these patients would be on this treatment for decades, long safety studies would be a pre-requisite.

Other infiltrating innate immune cells in PKD

Cell types other than macrophages have been observed in PKD. As such, $CD45^+$ and $CD4^+$ lymphocytes have been identified in the interstitium of ADPKD patients (84). Similarly, a few animal models of PKD such as kat^{2j}/kat^{2j} mice (103), Han:SPRD rats (104) and DBA/2FG-pcy mice (105) have reported the presence of lymphocytes or their markers in the cystic kidneys. The DBA/2FG-pcy mice develop ARPKD. Segmental dilation of the tubules (distal and collecting duct, similar to one seen in a UUO model) is evident at eight weeks of age and the kidneys get infiltrated with macrophages and lymphocytes at later stages (105). The significance of lymphocytes has not been specifically addressed or studied in PKD. However, $CD4^+$ T cells, in particular Th2 cells, have been shown to take part in promoting interstitial fibrosis in a rodent UUO model of kidney fibrosis wherein the tubular dilation is the first event to occur, followed by infiltration of immune cells into the kidneys (106-108). It should be noted that as mentioned earlier, PKD and UUO kidneys share a large number of genetic pathways that are upregulated (14, 86, 109). The most likely reason is that in PKD the enlarging cysts compress and obstruct normal healthy tubules, creating a virtual UUO-like situation, as well as microvasculature, which in turn evokes an inflammatory response, similar to that seen after ureteral ligation in the UUO model (14, 109). Depletion of macrophages or $CD4^+$ T cells results in better-preserved renal parenchyma and reduced fibrotic response in the UUO model. Lymphocytes also produce cytokines (interferon-γ and TNF-α following renal injury that can provide further inflammatory insult to the tissue (110-112). Thus, one could envision a similar role for lymphocytes in ADPKD, although more experimental evidence is necessary.

Mast cells in PKD

An acute inflammatory response can co-exist with chronic inflammation due to simultaneous tissue destruction and repair processes. One example is that of the presence of mast cells, although they are typically associated with an allergic response. Mast cells, surrounded by chymase, have been observed in the kidneys of end-stage ADPKD patients (113). Chymase was present in the interstitial fibrotic tissue. Chymase is not only a chemoattractant for inflammatory immune cells but can convert angiotensin I to angiotensin II (AngII) suggesting the potential of generating Ang-II in ADPKD kidneys, independent of angiotensin-converting enzyme (ACE) and could further contribute to the associated hypertension in PKD. Ang-II also acts as a chemoattractant for inflammatory cells and can activate NF-κB as well as MCP-1

expression by activating pro-inflammatory genes (114, 115). Interestingly, kidneys of the mice treated with Ang-II showed polycystic appearance along with inflammatory reactions in the tubules as well as glomeruli. Gene expression studies revealed upregualtion of Renin-1 (*Ren1*) and peroxisome proliferator-activated receptor (PPAR)-γ in the kidney tissue (116). Besides, adhesion molecules such as ICAM-1 and VCAM were upregulated, further facilitating infiltration of inflammatory cells. Ang-II has also been shown to stimulate formation of reactive oxygen species (ROS) that are known to cause tissue damage. Intrarenal Ang-II levels are also upregulated in the UUO model (117). Thus, mast cells harbor the potential for contributing to the disease progression of ADPKD, at least via chymase and Ang-II production. However, whether they would play a role during early or late stage of ADPKD remains to be determined.

Complement -3 in PKD

Following tissue injury, the renin angiotensin system (RAS) is also activated by complement-3 (C3) that induces partial dedifferentiation of the epithelial cells which then produce renin through induction of liver X receptor-alpha (LXRα). Recent studies have linked complement activation to cystogenesis. Indeed, gene expression analysis of the ARPKD model revealed dominance of complement system factors that can activate macrophages, including the major complement component C3. This was confirmed by increased C3 protein levels in the epithelia of three different rodent models of ARPKD and human ARPKD (63). Transcriptional dysregulation of complement genes has also been reported in the cells that line the cysts in ADPKD (65). These data were further bolstered by human validation by showing the presence of antigenic C3 in the cyst-lining epithelial cells of ADPKD and C3 activation fragments in renal cysts and urine from ADPKD patients (118). The iC3b fragment was one of the most abundant forms of C3 detected in cyst fluid and urine of ADPKD as well as that of ARPKD patients (119). The authors suggested that while various components of the complement system could act via different receptor pathways, the activation fragment iC3b that is a major macrophage antigen-1 (Mac-1) ligand, likely plays a central role in attachment, survival and differentiation of macrophages. This raises the possibility that iC3b might partly be responsible for cystogenic effects of macrophages. Partial evidence in support of cystogenic role of the complement system was provided by a recent study that observed an over-activated alternative complement system in ADPKD. Specifically, screening of the glycoproteome of urine samples of ADPKD patients showed highly-upregulated levels of complement factor B (CFB) and C9 besides serpin peptidase inhibitor and complement 1 inhibitor (SERPING1). The gene expression was validated by increased protein expression of CFB and C9 in cystic kidneys from ADPKD patients (120). However, the levels of those in serum were not altered. More importantly, the authors provided data to support the relevance of complement activation in progression of PKD in two separate rodent models of PKD, *Pkd1*$^{-/-}$ mice and Han:SPRD Cy/+ rats. To determine the role, if any, of complement in the disease progression, these animals were treated with the complement inhibitor, rosmarinic acid (RMA). Similar to the results from macrophage depletion studies, RMA administration in mice reduced the cystic index by ~ 60% that

was accompanied by significantly improved renal function. Similar results were observed in Cy/+ rats. Lower number of inflammatory cells as well as fewer $Ki67^+$ cyst-lining cells was observed that was accompanied by reduced interstitial fibrosis. Whether the beneficial effects observed in this study are largely attributable to reduced macrophage burden remains to be determined. In that regards, a recent study that used an inhibitor of MCP-1 synthesis (Bindarit) in *pck* rats, did not show any effect of cyst progression while it did improve proteinuria and renal function. In this particular study, a 40% reduction of macrophages was achieved (121). The lack of improvement in the cystic index could be attributed to the fact that a greater reduction in macrophage numbers may be necessary to achieve any impact on cell proliferation or cyst expansion. Alternatively, it may simply mean that quenching the pathways of macrophage activation is more critical. These aspects will have to be taken into account when considering any therapy targeting macrophages either directly or indirectly. Thus, experimental evidence is gradually emerging that supports the idea that inflammation could play an important, although not the primary, role in cyst progression in PKD. This role may be directly dependent as well as independent of the altered PC1 signaling in PKD.

Mechanisms regulating immune cell infiltration in PKD

For immune cells to traffic to the site of tissue injury, cells must egress from the bone marrow, or may already be circulating such as PBMCs. They then traverse through the blood vessels, attach and crawl through the endothelium at the specific site of injury into the interstitium. A chemotactic gradient must exist for directed migration of these cells and equally important are the endothelial adhesion molecules such as ICAM-1 and VCAM. Once at the site of injury, the local milieu will determine the activation state of these cells, in particular monocytes/ macrophages. The first step has to be up-regulation of a chemoattractant. Using magnetic resonance imaging (MRI) to detect macrophage trafficking in a mouse UUO kidney, we observed that extremely few macrophages traffic to an unobstructed kidney while the UUO kidney gets inundated with these cells (Yuan, Sherman, Karihaloo and co-workers, unpublished observation ; Figure 2). Following UUO, the obstructed kidney up-regulates the expression of chemoattractants such as MCP-1 and SDF1-α (109) that is similar to the response observed following an ischemic renal injury (122, 123). In PKD, an increased expression of chemoattractants is observed too. However, the difference being that inflammatory markers are seen upregulated even before cyst formation is visible, although the latter could be attributed to the limits of detection methods. For example, a cyst that is 400 μm in diameter is below the limit of current radiological detection (124). Nearly, three-fold increase in urinary MCP-1 level is observed in ADPKD patients with normal serum creatinine and urinary protein excretion (61). However, a recent study in a slowly progressing PKD model of *pcy* mice that have a mutated NPHP3 gene detected an increase in urinary MCP-1 after having detected microalbuminuria (125). In contrast, studies in the *pck* rats model of PKD detected an increased in MCP-1 already at postnatal week five (121), at which point no formal cysts are observed in this model but the tubules are dilated (126).

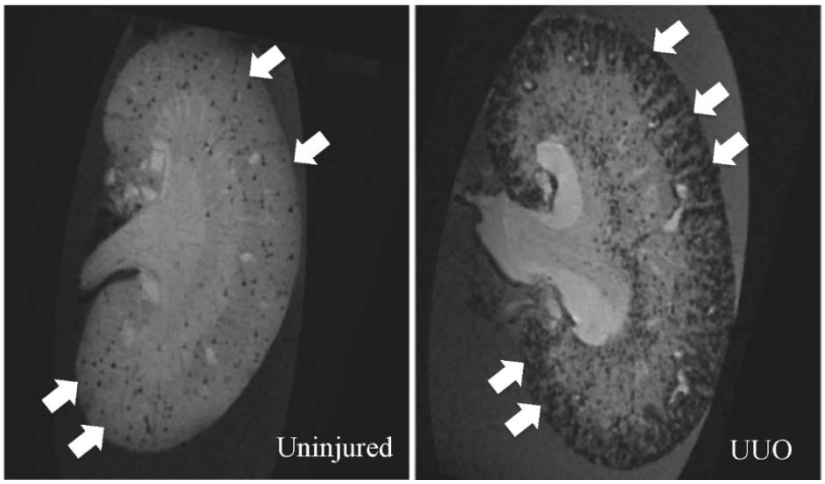


Figure 2. MRI imaging of monocytes tracking to kidney after unilateral ureteral obstruction (UUO). Bone-marrow (BM)-derived monocytes/macrophages were incubated with micron-sized iron oxide particles which they phagocytose. C57/Bl6J mice underwent UUO. 24 hours later, mice were injected these BM-derived iron-oxide containing macrophages and 24 hours after that, mice were sacrificed, kidneys were harvested and processed for MRI imaging. The black dots (white arrow heads) seen in the picture represent the macrophages. Very few macrophages traverse the uninjured kidney while most traffic is to the injured kidney – visible in both cortex and medulla.

Taken together, the aforementioned studies suggest that a change in the expression of a chemoattractant can occur due to multiple stimuli that may be initiated by the cell injury, such as ischemic injury to the kidney, or change in cell-shape as in tubular dilation of UUO or PKD, and/or due to dysfunctional PCs (discussed below).

Polycystin-dependent mechanisms

Others and we have shown that renal tubular epithelial cells lacking PC1 or cells carrying a mutation in *Pkd1* express and secrete significantly higher amounts of MCP-1 *in vitro* and *in vivo*, both in animal models of PKD as well as human ADPKD-derived cells (61, 86, 87). An unbiased systems biology approach for profiling human PKD1 cysts revealed a profile rich in immune and inflammatory responses (65). What this means is that, normally, PC1 would be suppressing any inflammatory responses, and the lack of PC1 or dysfunctional PC1 would release the brakes. Ma and co-workers answered this question when they determined that loss of cilia suppressed cyst growth upon inactivation of polycystins, thereby affirming that PCs are negative regulators of cystogenesis (42). One of the questions then arises, "Does PC1 modulate immune cell trafficking by directly regulating the expression of chemoattractants, such as *Mcp-1*. If yes, how?" While no direct evidence exists to date, we will discuss some potential mechanisms that could support the idea that PCs could directly regulate the expression of chemoattractants.

PC1-C-terminal tail (PC1-CTT) can modulate activity of transcription factors

PC1 undergoes multiple proteolytic cleavages that release both N-terminal extracellular domain and the C-terminal tail (PC1-CTT) (127, 128). To date three cleavages have been reported in the cytoplasmic C-terminal tail of PC1 releasing fragments of different sizes (129-132). The larger 35-kDa fragment accumulates in the nucleus as a result of reduced flow in the rodent kidney (129, 130). It was later determined that PC1-CTT undergoes γ-secretase-dependent cleavage, translocates to the nucleus where it regulates both proliferative and pro-apoptotic signaling pathways by modifying the interactions of transcription factor(s) with the transcriptional co-activator p300 (133). Specifically, it binds to TCF that is activated by β-catenin in response to Wnt ligand to induce-β-catenin pro-proliferative target genes. The binding of PC1 to TCF prevents its interaction with p300 a key transcriptional co-regulator for TCF, thereby acting as an inhibitor of TCF-mediated gene expression and a negative modulator of the Wnt signaling pathway. This 35 kDa PC1-CTT also binds to transcription factor CHOP that partly regulates the apoptotic pathway. CHOP too requires p300 for it to function. PC1-CTT binds to CHOP and prevents its association with p300 thereby reducing its activity. Expressing PC1-CTT in *Pkd1*-null cells provided the biological relevance of these interactions when it rescued increased proliferation and apoptosis of these cells *in vitro*. In the same study, expression of PC1-CTT in zebrafish larvae corrected the dorsal body curvature produced by the loss of PC1 and administration of a γ-secretase inhibitor. Furthermore, using a co-activator trap screen, they determined that several other transcription factors, including pro-apoptotic CHOP-10/GADD153, were significantly regulated by PC1-CTT.

One of those transcription factors is the activating transcription factor 4 (ATF4) (133) that is an ER stress-induced transcription factor. Interestingly, ATF4 stability and transcriptional activity is modulated by p300 (134) and just recently ATF4 was shown to modulate MCP-1 in microvascular endothelial cells (135). This raises an intriguing possibility that PC1-CTT, under a normal state, may negatively regulate MCP-1 expression by potentially preventing the interaction between ATF4 and p300. This needs to be confirmed experimentally. Transcription factor regulator C/EBPβ regulates the expression of another macrophage chemoattractant, SDF1-α (136). *Sdf1-a* is upregulated by renal tubules and endothelium of an injured kidney (109). Interestingly, PC1-CTT also interacts with C/EBPβ raising the possibility that PC1-CTT can directly regulate yet another chemoattractant. Once again, experimental confirmation has to be provided. Some of these possibilities are summarized in Figure 3.

Polycystin-independent mechanisms

The cyst development begins with focal monoclonal expansion of tubular cells that underwent a second hit. As the cells continue to proliferate, the cyst bulges out as a pouch eventually separating from the tubule (14). These cysts push on the neighboring tubules and microvessels creating a virtual obstructive nephropathy. Simple change of cell shape, such as in a dilated tubule, leads to partial dedifferentiation of the tubular cells as also happens in an obstructed tubule. We recently reported that these partially dedifferentiated cells (in a UUO kidney) acquire semi-mesenchymal-like phenotype and turn on the

expression of *Mcp1, Sdf1-a, Pdgf-a, Tgf-β1* etc,(109). An innate immune response is triggered to allow macrophages/monocytes home into an injured area directed by the gradient of MCP1/SDF1-α and other chemoattractant molecules. It should be noted that activated macrophages, endothelial cells and vascular smooth muscle cells are capable of producing MCP-1 to reinforce trafficking of additional monocytes/macrophages to the site of inflammation (137). Of note, dedifferentiation of the cyst-lining epithelial cells was also observed in an orthologous *pck* rat model of ARPKD. This was accompanied by an increase in the interstitial fibrosis markers, a hallmark of chronic inflammation (138). These data are further validated by unbiased gene profiling of cysts from PKD1 human polycystic kidneys. PKD1 cysts presented a profile that was rich in genes associated with kidney development, a sign of dedifferentiation/re-differentiation, as well as epithelial-mesenchymal transition (65).

The inflammatory response, once initiated, may feedback upon itself creating a vicious loop. In addition to PC1 dysfunction and/or cell shape change, the complement system is excessively activated in the cyst-lining cells of PKD (discussed earlier) as well in UUO tubular cells. C3 activation leads to generation of renin that in turn increases intra-renal Ang II (117). Ang II in turn induces the expression of adhesion molecules including ICAM-1 and VCAM-1 and chemokine MCP-1(116).

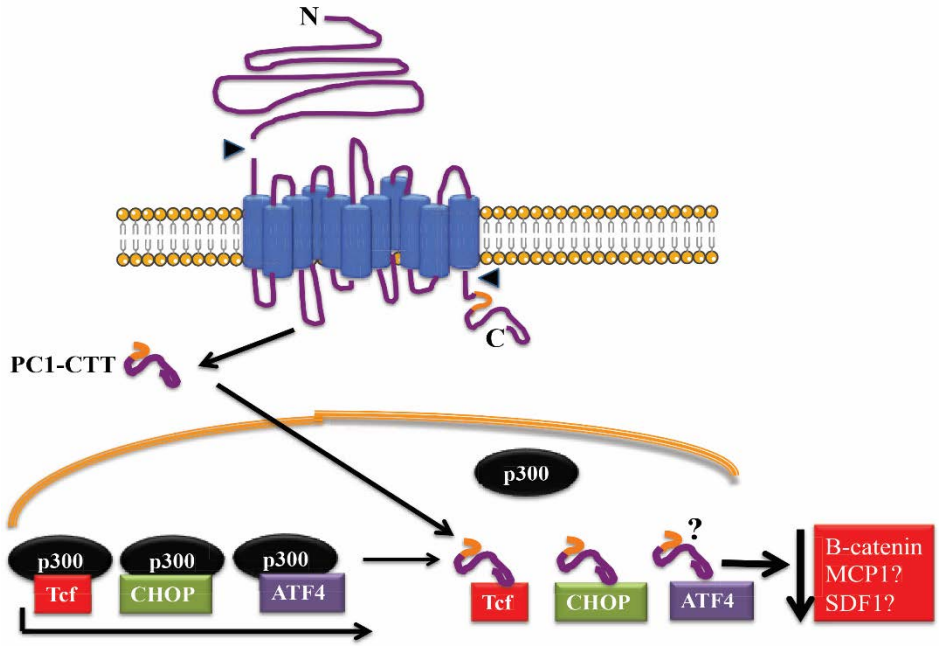


Figure 3. The cartoon shows potential mechanism by which PC-1 may modulate transcription. PC1 undergoes cleavage at the N and C-terminus (indicated by arrow heads). The C-terminal tail (PC1-CTT) translocates to the nucleus where it binds TCF, CHOP (confirmed) and ATF4 (speculated) to control transcript of β-catenin-dependent targets (confirmed) and MCP1 and/or SDF-1α transcription (speculated).

In addition to the above mentioned mechanisms, tubular cells of a PKD kidney (Hans:SPRD rat) are known to have an increased expression of osteopontin that too harbors monocyte/macrophage chemoattractant properties (139). Thus, immune cells may traffic to a PKD kidney to cues that are generated in a PC1-dependent and/or independent manner.

Macrophage activation

Macrophage activation can be classified into two categories: classically activated M1 and alternatively activated M2. This classification has been largely guided by responses (*in vitro*) to the prototypic T-helper 1 (Th1) cytokine, interferon-gamma (IFN-γ **or** Th2 cytokine interleukins 4 (IL-4) and 13 (IL-13) (140).

M1 macrophages are proinflammatory first responders whose job is to clear debris and apoptotic cells. Upon ligation with its receptor on macrophages, IFN-γ activates Janus kinase (JAK)1/2 and STAT-1 inducing a proinflammatory battery of chemokines, MCP-1 and monokine induced by gamma interferon (MIG) that together help recruit monocytes and T cells to the site of injury and inflammation (141). However, *in vivo*, in a sterile injury, DAMPs such as adenosine triphosphate (ATP) or nucleic acids that are released by the injured tissue, interact with their pattern-recognition receptors (PRRs) such as TLRs (142) and induce macrophages to a proinflammatory M1 state. Ligation of DAMPs by PRRs activates transcription factors such as NF-κB, augmenting the levels of proinflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-12 (74, 143). Thus, infiltrating monocytes differentiate into proinflammatory M1 macrophages via activation of STAT1 and TLR/NF-κB pathways. As mentioned earlier, M1 macrophages can exacerbate tissue injury (79). M1 macrophages are highly phagocytic and therefore help clear apoptotic cells and cell debris as an obligatory step to initiate tissue repair by M2 macrophages.

M2 macrophages hold a very diverse functional portfolio. They participate in wound healing but can also promote fibrosis and can be identified by IL4-induced expression of arginase-I (ARG1), mannose receptor (MR), Ym1 and insulin-like growth factor -1 (IGF-1), reviewed elsewhere (144). IL-4 (as well as IL-13) signal through IL-4Rα and activate the STAT6 pathway that in turn regulates ARG1 and Ym1. Interestingly, STAT6 engages with transcriptional co-activator such as C/EBP-β (135, 145). Yet another study indicates that p300/CBP too interacts with STAT6 and is necessary for IL-4-induced transcription of STAT6 (146). This raises the possibility that under healthy conditions, PC1-CTT while interacting with p300 could suppress STAT6 expression or signaling, similar to suppressing β-catenin-mediated transcription, and in the setting of loss of PKD1/2 or dysfunctional PC1/2, the inhibitory effect would be lost resulting in an overexpression/activation of STAT6. Indeed, Olsan and co-workers have demonstrated increased expression of STAT6 in cyst-lining epithelial cells in mouse PKD models (147). They also reported the presence of IL-13 (ligand) in cyst fluid and the overexpression of IL-4/13 receptor that would result in sustained activation of STAT6. Ablation and inhibition of STAT6 led to blunting of cystic expansion (147). However, macrophage accumulation or activation was not evaluated in

this study. One must also keep in mind that the experimental evidence also suggests STAT6-independent mechanisms for alternative macrophage activation (79).

As described above, M1 macrophages switch to the anti-inflammatory M2 pro-repair or pro-fibrotic phenotype. The kidney epithelial-derived factors that can facilitate this switch are not, as yet, very well defined. However, colony stimulating factor-1 (CSF1) is one factor that has been implicated in the switch, at least in part. More recently, granulocyte-macrophage (GM)-CSF was demonstrated to induce alternative activation of macrophages, following ischemia-reperfusion injury (148). Swenson-Fields and co-workers demonstrated that epithelial cells from human ADPKD cysts (as well as conditioned medium from these cells) promote distinct M2 differentiation of naïve as well as polarized macrophages and this effect was more potent than non-cystic tubular cells (87). These data provide a proof of concept that cyst-lining ADPKD cells must secrete soluble factor(s) that have the potential for inducing naïve or polarized macrophages to an alternative phenotype that is pro-repair but also pro-fibrotic.

Thus, there is reasonable evidence to suggest a direct role of PC1 in regulating chemokine/cytokine expression that facilitates the trafficking of innate immune cells to the cyst-lining cells in a polycystic kidney. There is sufficient evidence documenting the abundance of M2 type macrophages in ADPKD. There is also evidence that soluble factors derived from ADPKD cyst-lining cells can induce naïve or already polarized macrophages to M2, pro-repair/pro-fibrotic phenotype. This is very similar to what has been described in an ischemia-reperfusion model (discussed earlier) where M1 macrophages switched to an M2 activation state to facilitate repair by inducing tubular cell proliferation (79). However, the questions that have not yet been answered are: "What other factors are responsible for the macrophage phenotypic switch and the tubular cell proliferative response? Does PC1 directly modulate their expression in any way"? While currently we do not have answers to these questions, there are data demonstrating transcriptional regulatory properties of PC1, which raises the potential possibility that PC1 could indeed regulate the expression of some of those (as yet undefined) factors. Of note, ~15 kDa and ~30kDa PC1-CTT fragments have been found to accumulate in ADPKD patient kidneys. These complexes regulate transcriptional pathways and the activation of STATs as we described above (132). We now discuss evidence that suggests PC1-mediated STAT activation in non-lymphoid cells.

PC1 regulates activity of STATs in non-lymphoid cells

The STAT family of transcription factors is activated by JAK and plays a role in modulating immune responses, cell survival and differentiation. Activation of STATs leads to their binding to phospho-tyrosine residues of the receptors of activated growth factors or cytokines followed by STAT phosphorylation via receptor tyrosine kinases such as JAK or non-receptor tyrosine kinase like Src. Soon after, nuclear translocation follows where STATS carry out their diverse transcriptional regulatory functions (149). Of the six known STAT family members, only STAT3 and STAT6 have been shown to play some role in cyst progression of ADPKD.

The very first evidence of modulation of STAT activity by PC1 emerged when it was shown that overexpression of PC1 binds JAK2, activates STAT1 and induces cell-cycle arrest by up-regulating p21 (waf1) (150). Subsequently, Low and co-workers discovered that PC1-CTT undergoes cleavage, releases a ~ 17kDa PC1-CTT fragment that translocates to the nucleus, interacts with STAT6 transcriptional co-regulator p100, and co-activates STAT6-dependent gene expression (131). The same group later determined that PC1 activates STAT3 (132) that is in part dependent on Src. It was determined that membrane-anchored, full-length PC1 binds JAK2 and activates STAT1 and STAT3, and the cleaved CTT co-activates STAT1, STAT3 and /or STAT6 (151). It is important to note that cleaved CTT by itself does not activate STATs but can co-activate previously activated STAT, such as by a specific by growth factor, thereby amplifying the signal.

Both, STAT3 and STAT6 are aberrantly activated in cyst-lining cells of rodent PKD models. Pharmacological inhibition of STAT3 or STAT6 and genetic ablation of STAT6 slows down the cyst growth in these PKD models (147, 152, 153). These studies clearly highlight the significance of these two transcription factors in PKD. However, eventually their clinical significance will be judged by their relevance to human PKD patient population. For detailed description of the role of PC1 in modulating transcription the readers are directed to (154, 155). It should be noted that global gene analysis on human PKD1 renal cysts has revealed that, of the 100 most upregulated genes, 11 were associated with the JAK-STAT pathway while three were linked to the NF-κB pathway (65).

NF-κB and PKD

NF-κB is a complex of proteins that, in response to stress such as free radicals, controls cytokine production and cell survival. Aberrant NF-κB regulation is linked to inflammatory and autoimmune diseases and can be activated by stimulation of TLRs (156). Generally, NF-κB is associated with the acute phase of inflammation wherein upon stimulation, the p65 subunit (normally located in cytoplasm) of the NF-κB complex gets phosphorylated, translocates to the nucleus and initiates transcription (157). The cytokines regulated by NF-κB include TNF-α, IL-1α and β, IL-6, Ccl3, Ccl4 and MCP-1 (158). Of these, TNF-α, and IL-1β can also activate the NF-κB pathway, thereby creating a self-perpetuating feedback loop (159). A few studies have demonstrated the importance of NF-κB pathway in PKD, discussed below.

It was discovered that cells lacking *Pkd1* have higher amounts of phosphorylated p65 that indicates activated NF-κB (160). Subsequently, phosphorylated NF-κB protein was detected in the nuclei of cyst-lining cells in a mouse PKD2 model as well as in human ADPKD kidneys (161). Coincidentally, the receptors of advanced glycation end product (RAGE) and s100a8/9 levels were found to be elevated in PKD2 mice (161). RAGE is a mediator of NF-κB and is activated not only in CKD (such as in diabetic nephropathy) but in neuroinflammation as well (162). Recently, Qin and co-workers reported that hyperactivated c-Met (the hepatocyte growth factor/HGF receptor) in mice lacking *Pkd1* led to increased NF-κB signaling which in turn upregulated the expression of Wnt7a and

Wnt7b that are involved in cell proliferation. Inhibiting the Wnts led to a decrease in cystic area (160). TNF-α, a target gene of the NF-κB pathway, induced cyst growth in explanted kidneys in $Pkd2^{+/-}$ and wild type kidneys suggesting that TNF-α can directly incite cystogenesis (60). Together, these data provide some evidence that support a role for NF-κB in ADPKD. Further studies would have to be conducted to firmly establish a role for this pathway in the progression of ADPKD.

Significance of chronic inflammation in PKD

There is a wide variability in the rate of decline in renal function and progression to ADPKD. While it is undoubtedly influenced by the specific mutation, gene dosage and epigenetics, sustained chronic inflammation could be yet another factor influencing the rate of progression of ADPKD. Inflammation seems to correlate with disease initiation and progression, given that it is present even before any noticeable functional alteration and continues to be present in the late stages as well. Data discussed above suggest that inflammation may even promote cystogenesis via its effector cellular components, such as macrophages, and a complementary activation of certain signaling cascades, such as NF-κB and TNF-α. There is also some evidence in the literature that suggests targeting inflammation may have beneficial effects in the PKD patient population. For example, drugs that are typically used for controlling hypertension, angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs) may have anti-inflammatory benefits as well. They have been shown to lower markers of inflammation in hypertensive ADPKD patients (163). Similarly, an improved renal function correlates with reduced inflammatory cell infiltrate (86, 87). It will be interesting to find out whether a nearly 50% reduced kidney growth rate (18) in Tolvaptan-treated patients translates to corresponding lesser inflammation as well. A list of compounds with potential anti-inflammatory effects has been provided by Ta and co-workers elsewhere (10).

An additional factor to be considered is interstitial fibrosis that goes hand in hand with inflammation. Indeed, fibrosis is a hallmark of chronic inflammation. While it is beyond the scope of this chapter to discuss the potential role of fibrosis in ADPKD, there is no doubt that fibrosis is detrimental to organ function. Indeed, tubulointerstitial fibrosis and not the glomerular lesions was found to be a significant predictor of renal prognosis (164) in type II diabetics. The potential role of fibrosis in PKD is described elsewhere (165).

Conclusion

Taken together, the current evidence suggests that inflammation begins very early in PKD, potentially even before any overt cyst growth, and seems to correlate with the progression of disease. Undoubtedly, the underlying mutation and the resultant dysfunctional PC1/2 is the basic cause for cystogenesis but inflammation could play

a very important role in cyst progression. This is supported by three experimental studies where a decrease in macrophage content led to an improved parenchyma, reduced cyst burden and improved renal function (86-88). However, targeting inflammation directly for therapeutic purpose in PKD (and CKD in general) poses challenges. For example, both active and chronic inflammatory pathways are activated concurrently, particularly in the late stages of PKD. Hence, one will have to maintain a fine balance between the good and the bad inflammation, knowing that, inflammation after all, is a friend as well.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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