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Inflammation and Fibrosis in Polycystic Kidney Disease

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Abstract

Polycystic kidney disease (PKD) is a commonly inherited disorder characterized by cyst formation and fibrosis (Wilson, N Engl J Med 350:151–164, 2004) and is caused by mutations in cilia or cilia-related proteins, such as polycystin 1 or 2 (Oh and Katsanis, Development 139:443–448, 2012; Kotsis et al., Nephrol Dial Transplant 28:518–526, 2013). A major pathological feature of PKD is the development of interstitial inflammation and fibrosis with an associated accumulation of inflammatory cells (Grantham, N Engl J Med 359:1477–1485, 2008; Zeier et al., Kidney Int 42:1259–1265, 1992; Ibrahim, Sci World J 7:1757–1767, 2007). It is unclear whether inflammation is a driving force for cyst formation or a consequence of the pathology (Ta et al., Nephrology 18:317–330, 2013) as in some murine models cysts are present prior to the increase in inflammatory cells (Phillips et al., Kidney Blood Press Res 30:129–144, 2007; Takahashi et al., J Am Soc Nephrol JASN 1:980–989, 1991), while in other models the increase in inflammatory cells is present prior to or coincident with cyst initiation (Cowley et al., Kidney Int 43:522–534, 1993, Kidney Int 60:2087–2096, 2001). Additional support for inflammation as an important contributor to cystic kidney disease is the increased expression of many pro-inflammatory cytokines in murine models and human patients with cystic kidney disease (Karihaloo et al., J Am Soc Nephrol JASN 22:1809–1814, 2011; Swenson-Fields et al., Kidney Int, 2013; Li et al., Nat Med 14:863–868, 2008a). Based on these data, an emerging model in the field is that disruption of primary cilia on tubule epithelial cells leads to abnormal cytokine cross talk between the epithelium and the inflammatory cells contributing to cyst growth and fibrosis (Ta et al., Nephrology 18:317–330, 2013). These cytokines are produced by interstitial fibroblasts, inflammatory cells, and tubule epithelial cells and activate multiple pathways including the JAK-STAT and NF-κB signaling (Qin et al., J Am Soc Nephrol JASN 23:1309–1318, 2012; Park et al., Am J Nephrol 32:169–178, 2010; Bhunia et al., Cell 109:157–168, 2002). Indeed, inflammatory cells are responsible for producing several of the pro-fibrotic growth factors observed in PKD patients with fibrosis (Nakamura et al., Am J Nephrol 20:32–36, 2000; Wilson et al., J Cell Physiol 150:360–369, 1992; Song et al., Hum Mol Genet 18:2328–2343, 2009; Schieren et al., Nephrol Dial Transplant 21:1816–1824, 2006). These growth factors trigger epithelial cell proliferation and myofibroblast activation that stimulate the production of extracellular matrix (ECM) genes including collagen types 1 and 3 and fibronectin, leading to reduced glomerular function with approximately 50% of ADPKD patients progressing to end-stage renal disease (ESRD). Therefore, treatments designed to reduce inflammation and slow the rate of fibrosis are becoming important targets that hold promise to improve patient life span and quality of life. In

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fact, recent studies in several PKD mouse models indicate that depletion of macrophages reduces cyst severity. In this chapter, we review the potential mechanisms of interstitial inflammation in PKD with a focus on ADPKD and discuss the role of interstitial inflammation in progression to fibrosis and ESRD.

12.1 Introduction

Polycystic kidney diseases (PKD) are a group of genetically inheritable disorders that are characterized by the formation of cysts in the kidney and other organs (Wilson 2004). Two forms of autosomal PKD exist, depending on their underlying genetic mutation. Autosomal dominant PKD (ADPKD) affects approximately 1 in 1000 people and is caused by a mutation in either *PKD1* or *PKD2*, which encode the polycystin-1 (PC1) or polycystin-2 (PC2) protein, respectively (Wilson 2004). Autosomal recessive PKD (ARPKD) affects 1 in 20,000 individuals and is caused by a mutation in *PKHD1*, which encodes the protein fibrocystin/polyductin (Wilson 2004). For both forms of the disease, the affected proteins localize to the primary cilia although both proteins are also found in regions outside of the primary cilium (Wilson 2004; Oh and Katsanis 2012). While the function of primary cilia in the kidney remains uncertain, it has been proposed that they are involved in mechanosensation to detect fluid flow through the tubule lumen, in regulation of cell proliferation and oriented cell divisions, as well as in cell-to-cell and cell-to-matrix signaling (Yoder 2007; Yoder et al. 2002; Zimmerman and Yoder 2015; Kotsis et al. 2013; Basten and Giles 2013). In ADPKD, cyst growth is associated with changes in epithelial cell proliferation and differentiation, fluid secretion, and basement membrane abnormalities (Wilson 2004). Expansion of cysts leads to obstruction and compression of surrounding nephrons that can significantly reduce kidney function (Grantham et al. 2011). During late stages of disease progression, cyst formation is accompanied by ECM deposition and fibrosis, further reducing glomerular filtration and eventually leading to ESRD (Wilson 2004; Wilson and Goilav 2007; Wilson and Falkenstein 1995). Importantly, disruption of primary cilia or the polycystins using a variety of mouse models causes cyst formation in the kidney and liver along with associated fibrosis in both organs (Yoder et al. 1995; Ma et al. 2013). Recently, in vivo studies using conditional cilia and polycystin mutant mice showed that the rate of cyst formation depends on the timing of gene deletion. Disruption of cilia or polycystin proteins prior to postnatal day 12–14 caused rapid cyst formation. In contrast, deletion of these proteins after postnatal day 14 caused slow focal cyst formation (Davenport et al. 2007; Piontek et al. 2007; Lin et al. 2003). However, the protracted rate of cyst formation in the adult-induced mutants can be greatly exacerbated by injury (Sharma et al. 2013; Takakura et al. 2009; Patel et al. 2008). Expression profiling data indicated there is an increased response to injury with marked elevation of innate immune response genes in cilia or polycystin mutant samples, leading to the idea that inflammatory cells are involved in PKD progression (Mrug et al. 2008). This is further supported by data showing reduced cystic pathology and improved renal function in mouse PKD models in which macrophages were depleted (Karihaloo et al. 2011; Swenson-Fields et al. 2013). The involvement of other inflammatory cell types in PKD is less understood. Inflammatory cells can serve as potent producers of pro-inflammatory, pro-mitotic, and pro-fibrotic cytokines; therefore, understanding the involvement of inflammatory cells in cyst formation and fibrosis and their

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relationship with signaling pathways regulated by the primary cilia located on the epithelium will provide innovative insights into the mechanism of disease progression. More important, this understanding will open new targets for therapeutic intervention to slow the progression of cystic kidney disorders in humans.

12.2 Inflammation in the Pathogenesis of PKD

12.2.1 Immune Cells in PKD

Accumulation of inflammatory cells in the renal interstitial space is becoming appreciated as a hallmark of human and animal models of PKD (Fig. 12.1a, b) (Ta et al. 2013; Grantham 2008). One of the most studied inflammatory cells is the macrophage. Macrophages are involved in innate immunity and in tissue development, repair, and homeostasis (Ginhoux et al. 2015; Wynn et al. 2013). In kidney, they express surface markers including F4/80, CD11b, and Ly6c in mice and CD14 and CD16 in humans, which are used to identify different subtypes of macrophage (Nelson et al. 2012). An interesting feature of macrophages is their ability to become polarized and express either pro-inflammatory or anti-inflammatory cytokines in response to signals found in the tissue microenvironment. This paradigm is supported by data showing two distinct responses to treatment with cytokines in vitro (Gordon and Taylor 2005; Mantovani et al. 2002). Macrophages stimulated with LPS or interferon-gamma demonstrate a pro-inflammatory Th1-like phenotype with potent antimicrobial and antitumor activity. This macrophage is referred to as the classically activated or M1-like macrophage. M1 macrophages are characterized by expression of iNOS, TNF-α, and IL-1β amongst others and have a pro-inflammatory function (Sica and Mantovani 2012; Benoit et al. 2008). On the other hand, naı̈ve macrophages treated with interleukin-4 or 13 produce an anti-inflammatory response and are referred to as alternatively activated or M2-like macrophages (Adams and Hamilton 1984). These M2 macrophages express arginase 1 and IL-10 and have anti-inflammatory and wound healing functions (Sica and Mantovani 2012; Benoit et al. 2008). However, several in vivo studies demonstrated that macrophages cannot be clearly defined into either M1- or M2-like states, but have a wide degree of plasticity depending on their environment (Helm et al. 2014; Kratochvill et al. 2015; Stables et al. 2011; Xue et al. 2014; Ginhoux and Jung 2014; Lavin et al. 2014). It is now believed that macrophages which are present in vivo display a range of phenotypes that fall somewhere in between the M1 and M2 spectrum and that they are able to rapidly switch these phenotypes based on external cues. Intriguingly, evidence suggests that M1 macrophages can transition to an M2-like polarization following phagocytosis of necrotic or apoptotic cells (Huen and Cantley 2015; Fadok et al. 1998) or when cultured with renal epithelium demonstrating the importance of the tissue microenvironment on macrophage polarization (Swenson-Fields et al. 2013).

The origin of macrophages in specific tissues is an area of intense debate. The old model regarding macrophage origin suggests that all macrophages present in tissue can be maintained from a constant supply of bone marrow-derived circulating monocytes (van Furth and Cohn 1968; Katz et al. 1979). However, the new model of macrophage origin has demonstrated that there are two distinct populations of macrophages that can be distinguished by their progenitors, developmental history, and renewal mechanisms (Schulz

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et al. 2012). One subtype of macrophage is derived from bone marrow progenitor cells and is referred to as monocytes or infiltrating macrophages (in mice F4/80^{lo} and Cd11b^{hi}) once they reach their destination organ (Schulz et al. 2012; Merad et al. 2002; Ginhoux et al. 2010). In contrast, tissue-resident macrophages (in mice F4/80^{hi} and Cd11b^{lo}) develop in the yolk sac, enter tissues early during development, and originate from embryonic progenitors (Schulz et al. 2012). The yolk sac-derived macrophages persist in some adult tissues (e.g., epidermis, liver) independent of bone marrow-derived hematopoietic stem cells (HSCs) (Schulz et al. 2012; Ginhoux et al. 2010). They can self-proliferate in response to growth factors such as CSF-1 and other proliferative cytokines (Ginhoux and Jung 2014). In normal kidney, about half of the resident macrophages are derived from the yolk sac and maintained through self-renewal while the remainders are derived from the hematopoietic lineage (Schulz et al. 2012). Resident renal macrophages have important developmental roles influencing ureteric bud branching, producing cytokines, and monitoring surrounding cells for abnormal cell death (Rae et al. 2007; Pollard 2009). The second distinct population of renal macrophage, the infiltrating macrophage, rapidly accumulates in the kidney in response to injury (e.g., following renal ischemia–reperfusion injury; IRI), produces large amounts of pro-inflammatory cytokines, and is associated with worsened kidney injury and fibrosis. Bone marrow-derived infiltrating macrophages can be further classified based on expression of the surface marker Ly6c (Ly6c^{hi}, Ly6c^{int}, Ly6c^{lo}) (Clements et al. 2015; Lin et al. 2009). Following IR injury, Ly6c^{hi} infiltrating macrophages present in the kidney and produce pro-inflammatory cytokines (Clements et al. 2015). Several days after infiltration, these Ly6c^{hi} macrophages downregulate expression of Ly6c (Ly6c^{lo}) associated with kidney repair and production of extracellular matrix genes (Lin et al. 2009). Despite functional similarities to M1 and M2 macrophages, gene expression analysis comparing Ly6c^{hi}, Ly6c^{int}, and Ly6c^{lo} macrophages to M1- and M2-like macrophages indicates that these populations do not fit into the canonical M1/M2 classification (Clements et al. 2015).

Both infiltrating and resident macrophage numbers increase in PKD. While data indicate that macrophages impact the rate of cyst formation based on depletion studies in mice, it is not clear whether inflammation is important for cyst initiation or is simply a consequence of the pathology (Ta et al. 2013). In the Lewis polycystic kidney (*lpk*) and *pck* rats, data indicate cysts are present prior to the increase in inflammatory cells (Phillips et al. 2007; Takahashi et al. 1991); however, in Han: SPRD rats inflammatory cells are present prior to or coincident with cyst initiation (Cowley et al. 1993, 2001). Furthermore, using a heterozygous ADPKD mouse model exposed to IRI, two groups demonstrated an increased number of neutrophils, macrophages, and pro-inflammatory cytokines prior to cyst formation (Bastos et al. 2009; Prasad et al. 2009). The functional importance of macrophages in cystic disease progression was demonstrated by depletion of macrophages using liposomal clodronate (LC), a phagocytic poison that leads to macrophage death. Treatment of mice with LC improved cystic indices and renal function compared to controls, suggesting that macrophages do have a role in promoting cyst formation (Karihaloo et al. 2011; Swenson-Fields et al. 2013).

The overlap between resident and infiltrating macrophage populations in mice and humans remains uncertain as many of the macrophage surface markers are not shared between species. In human PKD, CD68-positive macrophages, which resemble M2-like or resident

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macrophages in mice, are present in the renal interstitium of ADPKD patients at both early and advanced stages of kidney disease (Zeier et al. 1992). More recently, HAM56 (a marker for human macrophages)-positive macrophages were shown to be distributed throughout the interstitium of kidneys from ARPKD and ADPKD patients including sites adjacent to cysts. However, the ratio of M2-like macrophages out of total macrophages was similar between control and PKD kidneys (Swenson-Fields et al. 2013), suggesting that the markers used in this study were not specific for human M2-like macrophages or that the ratio of M2-like macrophages was unaltered in the cystic kidneys. Interestingly, epithelial cells derived from control and cystic human kidneys produced soluble factors which induced polarization of macrophages to an M2-like phenotype in vitro (Swenson-Fields et al. 2013). However, marker characterization studies of the M2-like macrophages found within ADPKD kidneys have not revealed the origins of these macrophages (yolk sac or bone marrow derived). The M2-like macrophage response in mice was first noted in a rapidly progressive model of ARPKD, the Cys1-cpk mouse (Mrug et al. 2008); however, when these macrophages enter the kidney remains controversial. In contrast, CD-68 (ED-1)-positive macrophages have been detected in heterozygous Han:SPRD-Cy rats when cystic dilatations were initiating, suggesting a possible causal rather than a responsive role for macrophages in cyst development (Cowley et al. 2001). Subsequent studies using the *PKD1*$^{fl/fl}$; Pkhd1-Cre mouse also demonstrated the presence of alternatively activated macrophages based on expression of surface markers (F4/80+, CD45+, CD11c−) and low levels of Ly6C (Ly6C^{lo}) (Karihaloo et al. 2011).

The involvement of other immune cells such as T lymphocytes, mast cells, and neutrophils has been reported in human PKD patients and rodent models (Zeier et al. 1992; Ibrahim 2007; Takahashi et al. 1991; Vogler et al. 1999; Kaspareit-Rittinghausen et al. 1989; McPherson et al. 2004; Bernhardt et al. 2007). Currently, there is significant debate about the presence of dendritic cells in the kidney. Several groups have shown that dendritic cells are present in the kidney based on their surface expression of CD11b, F4/80, and CD11c (Li et al. 2008b; Hochheiser et al. 2013; Hull et al. 2015). However, CD11c has also been reported to be expressed by tissue-resident macrophages, raising the possibility that resident macrophages and dendritic cells may be overlapping populations (Cao et al. 2015). In addition to macrophages, the number of CD4-positive T cells is increased in the interstitial space of ADPKD patients and in animal models of PKD (Zeier et al. 1992; Takahashi et al. 1991; Vogler et al. 1999; Kaspareit-Rittinghausen et al. 1989). Furthermore, it is believed that mast cells may be involved in PKD progression through production of pro-inflammatory molecules including chymase and AngII (McPherson et al. 2004; Nadel 1991; Dell'Italia and Husain 2002). Finally, an elevated number of neutrophils have been reported in human and canine cystic kidney disease models (Bernhardt et al. 2007; O'Leary et al. 1999). However, conclusions about the contribution of neutrophils to disease pathogenesis are limited as the markers used for neutrophils in those studies have subsequently been shown to be non-neutrophil specific. While a wide variety of immune cells are increased in cystic models, their importance in cyst formation remains to be determined. Future studies should be directed at better defining these populations and their respective roles in cyst formation and fibrosis.

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12.2.2 Dysregulation of Chemokines and Cytokines in PKD

Chemokines are important for immune cell infiltration, activation, and polarization and in regulating immune cell behavior (Fig. 12.2b, c). Therefore, determining the involvement of chemokines and cytokines in mouse models of PKD will provide insight into their role in modulating immune cells and inflammation associated with cystic disease.

One of the best studied chemokines is MCP-1 (Ccl2), which binds to its cognate receptor, CCR2. CCR2 is a member of the CC chemokine family of G-protein coupled receptors and is typically expressed on the surface of monocytes or T cells (Li et al. 2008b; Bruhl et al. 2004). CCR2 mediates cell infiltration in renal inflammatory states such as diabetic nephropathy, glomerulonephritis, and ischemia–reperfusion injury. More important, MCP-1 is markedly elevated in the cyst fluid of ADPKD patients, and increased levels of MCP-1 are associated with worsened renal function and cystic disease outcome (Zheng et al. 2003). The increased expression of MCP-1 in mouse and rat models of PKD appears to parallel that observed in humans. In Han:SPRD rats, MCP-1 mRNA was elevated in homozygous mutant rats compared to wild-type controls (Cowley et al. 2001). Interestingly, heterozygous Han:SPRD cy/+ males displayed higher MCP-1 levels compared to females, which correlates with observations in humans that males often experience higher MCP-1 concentration in urine and serum than females (Cowley et al. 2001). In vitro models suggest that MCP-1 is produced by tubule epithelial cells as *PKD1*−/− tubule cells have significantly higher expression of MCP-1 compared to control cells. However, in a mouse adriamycin nephropathy model, data suggest that renal F4/80+ CD11c+ mononuclear phagocytes in kidney are also a major source of MCP-1 (Cao et al. 2015). Based on the increased MCP-1 expression across multiple cystic models and human patients, MCP-1 has been proposed as a biomarker for PKD. However, there is no evidence demonstrating a direct causative role for MCP-1 in disease progression as inhibition of MCP-1 signaling using Bindarit did not affect cyst formation (Zoja et al. 2015). Nevertheless, Bindarit treatment did reduce the renal accumulation of ED-1-positive inflammatory cells, suggesting that CCR2-mediated inflammatory cell infiltrates are not a critical component of PKD.

In addition to MCP-1, expression of several other chemokines/cytokines is increased in cystic kidney disease models. This includes osteopontin, IL-1beta, CCL6, CX3CL1, colony-stimulating factor 3 (CSF3), CXCL1, CSF1, CCL28, IL33, IL8, IL6, and IL17D and CXCL8 that function in the recruitment of myeloid-derived cells (macrophages, mast cells, neutrophils) into the cystic kidney. The importance of these chemokines in disease progression still needs to be thoroughly evaluated.

In contrast to the above cytokines, TNF-α appears to have a significant role in cyst formation (Fig. 12.2b, c). In human ADPKD cyst fluid, levels of TNF-α were dramatically increased compared to controls (Li et al. 2008a; Gardner et al. 1991). Using the *cpk* mouse model, Nakamura et al. demonstrated that cystic mice had increased expression of TNF-α mRNA compared to wild-type controls (Nakamura et al. 1993). Furthermore, TNF-α expression increased with age and cyst severity, suggesting that TNF-α accumulation is associated with cyst progression (Li et al. 2008a; Nakamura et al. 1993). Addition of TNF-α to cultured *PKD2*+/− and wild-type embryonic kidney explants induced cystogenesis that could be blocked by the TNF-α inhibitor etanercept (Li et al. 2008a). Inhibition of TNF-α-

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converting enzyme (TACE) led to a significant reduction in cystic index, serum creatinine, and BUN levels in the *bpk* mouse model of PKD (Dell et al. 2001). Taken together, these data implicate TNF-α as a key contributor to cyst formation.

12.2.3 Inflammatory Pathways in PKD

Recent studies in PKD disease models demonstrate that disruption of ciliary proteins specifically in the tubule epithelium causes cyst formation that is associated with an altered inflammatory response (Ta et al. 2013). Importantly, immune cells do not possess cilia, raising the possibility that cilia on tubule epithelium have a role in regulating inflammatory responses and that dysregulation of signals between the epithelium and inflammatory cells contributes to cyst development (Fig. 12.2) (Qin et al. 2012; Dinsmore and Reiter 2016; Wann and Knight 2012; Wann et al. 2014; Low et al. 2006). The signaling pathway involved and the potential role for either PC1 or PC2 in the inflammatory response are unknown although mice heterozygous for PC1 or PC2 show enhanced inflammation following renal injury compared to their wild-type littermates (Bastos et al. 2009; Prasad et al. 2009). The global gene analysis of human *PKD1* kidneys found that many inflammatory pathways are activated in PKD including the JAK-STAT pathway and the NF-κB signaling pathway (Song et al. 2009). NF-κB is an important inflammatory pathway activated in response to a variety of cytokines including TNF-α, IL-1β, IL6, and MCP-1 (Pahl 1999). Following ligand binding, phosphorylation of the NF-κB inhibitor, IκB, results in its degradation and subsequent activation and nuclear translocation of NF-κB. Data from several studies support a role for NF-κB in cyst formation (Qin et al. 2012). *PKD1* knockout epithelial cells have increased NF-κB-induced luciferase reporter activity and enhanced phosphorylation of the NF-κB subunit P65 compared to control cells (Qin et al. 2012). Furthermore, Park et al. demonstrated there is an increase of NF-κB protein and that it is phosphorylated in epithelial cells from *PKD2* knockout mice, but not in the control mice (Park et al. 2010). Collectively, these data indicate that upregulation of NF-κB pathway activity occurs in animal models of PKD. Wnt7b may function downstream of NF-κB as studies by Qin et al. showed that increased NF-κB signaling results in overexpression of Wnt7b, which is also present in *PKD1* mutant mice. Importantly, inhibition of NF-κb or Wnt7b results in a significant decrease in cyst severity in the *PKD1* mutant mouse and in organ culture models (Qin et al. 2012).

The JAK-STAT pathway is activated during inflammation and is believed to contribute to cyst formation as demonstrated by increased STAT3 activity in cyst-lining epithelial cells of PKD mutant animals (Fig. 12.2c) (Weimbs and Talbot 2013). In vitro and In vivo studies have shown that PC1 and PC2 are required for JAK1/2 activation and that the c-terminal tail of PC1 regulates STAT3 activation through the src tyrosine kinase (Talbot et al. 2014; Bhunia et al. 2002). The JAK-STAT pathway is also regulated by the suppressor of cytokine signaling (SOCS-1) which limits the inflammatory activity of macrophages. SOCS-1 knockout leads to the development of renal cysts in mice, but it is unknown whether this effect is mediated by inflammation or other contributions of the JAK-STAT signaling pathway (Metcalf et al. 2002).

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12.3 Fibrosis in PKD

12.3.1 Extracellular Matrix in PKD

The hallmark of tubule interstitial fibrosis is the accumulation of extracellular matrix (ECM) proteins such as collagen I and III (Zeisberg and Neilson 2010). Similar to many renal disorders, abnormalities in ECM accumulation were also found in kidneys from PKD patients and from orthologous animal models of PKD (Wilson et al. 1992; Wilson and Falkenstein 1995; Wilson and Sherwood 1991; Geng et al. 1999; Wilson and Burrow 1999; Guay-Woodford 2003; Wilson 2008). While ECM accumulation was often described in end-stage kidney disease (ESRD), abnormal ECM composition and increased basement membrane thickness were also observed in early-stage, pre-dialysis ADPKD patients (Wilson et al. 1992). This suggests that tissue remodeling and ECM deposition may be an essential component of cyst progression rather than simply being the result of cyst formation and inflammation. The ADPKD-associated changes include abnormalities in ECM production, composition and turnover, and differences in content of collagen types I, III, and basement membrane collagen type IV, fibronectin, and heparin sulfate proteoglycan (HSPG) (Wilson et al. 1992). These abnormalities were most commonly noted in regions surrounding cysts and interstitial fibroblasts (Norman 2011). While many factors may regulate the activity of pro-fibrotic pathways, recent studies in animal models indicate that polycystins may control production of ECM more directly and that inadequate regulation of this process is responsible for PKD-associated vascular abnormalities (Liu et al. 2014). Importantly, upregulation of the major pro-fibrotic growth factor, transforming growth factor β (TGF-β), was observed in *PKD1* haploinsufficient mice and loss of *PKD1* leads to increased responsiveness of the cystic epithelium and fibroblasts to TGF-β (Wilson et al. 1992; Song et al. 2009; Hassane et al. 2010). These observations may explain enhanced Smad2/3 nuclear localization observed in PKD patients and animal models (Hassane et al. 2010). Similarly, loss of polycystins is associated with notochord collagen overexpression in zebrafish that is thought to contribute to their body axis curvature defects (Mangos et al. 2010). Together, these data suggest that the PKD-associated changes in ECM composition may be a direct consequence of polycystin mutation.

12.3.2 Dysregulation of ECM Turnover in PKD

Development of fibrosis in PKD and other fibrotic models is dependent on both the amount of ECM that is produced and the extent of matrix turnover which occurs during disease progression (Norman 2011; Catania et al. 2007). Among the many factors that influence ECM turnover, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are perhaps the most extensively studied in PKD (Nakamura et al. 2000; Hassane et al. 2010; Catania et al. 2007; Schaefer et al. 1996; Obermuller et al. 2001; Rankin et al. 1996). Despite the clear evidence that MMPs are dysregulated in PKD, the importance and cause of these changes remains controversial. Schaefer and colleagues showed that MMP2 was present in proximal tubule cells from normal rat kidney but significantly decreased in the cystic Han:SPRD rat (Schaefer et al. 1996). This group also demonstrated that TIMP-1 and TIMP-2 mRNA levels were increased in the mutant rat (Schaefer et al. 1996). Paradoxically, MMP14 mRNA was increased in cyst-lining epithelia and distal tubules in the Han:SPRD rat (Obermuller et al. 2001). Inhibition of MMP activity

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with batimastat reduced cyst number and kidney weight suggesting a detrimental role for MMPs in cyst progression (Obermuller et al. 2001). Likewise, conditioned media from kidney tubule cells isolated from the *cpk* mouse contained elevated amounts of MMP-2, MMP-3, MMP-9, and TIMP1 (Rankin et al. 1996). The increased expression of MMPs in PKD models was recently confirmed by Hassane et al. who showed increased expression of MMP-2 using a *PKD1* mouse model of cyst formation (Hassane et al. 2010). In human ADPKD, patient serum contains increased levels of multiple MMPs, TIMPs, and plasminogen activator inhibitors (PAI) in both pre-dialysis and end-stage ADPKD kidneys (Nakamura et al. 2000). Data demonstrating an important role of the plasminogen activators and inhibitors in PKD are limited, although increased expression of PAI-1 has been reported in both mouse and human PKD samples (Norman 2011; Eddy 2009). It is believed that PAI are pro-fibrotic due to their ability to recruit macrophage and myofibroblasts to the tubulointerstitial area rather than their inhibitory effects on the serine proteases tPA and uPA (Norman 2011; Eddy 2009). Together, these data suggest that MMP expression is dysregulated in PKD and may lead to cyst progression by promoting ECM turnover and allowing expansion of cystic epithelial cells.

The functional consequences of changes in ECM-degrading enzymes in PKD are not fully understood. However, they likely include changes in cellular function and immune regulation. One mechanism of immune regulation may occur through breakdown of collagen I into a PGP fragment. PGP is a key regulator of inflammatory neutrophil accumulation, a process that is central to the pathogenesis of chronic obstructive pulmonary disease (Snelgrove et al. 2010). Since one of two MMPs that participate in generation of PGP is increased in ADPKD (MMP-9), PGP or other ECM collagen fragments may exert important immunoregulatory functions in PKD kidneys.

The interactions of cells with ECM or its breakdown products are mediated by matrix receptors including integrins and syndecans (Geiger et al. 2001). Following binding of ECM to these receptors, focal adhesion complexes form allowing for intracellular signaling to occur through a variety of pathways (Ehrhardt et al. 2002; Wozniak et al. 2004). To date, it has been demonstrated that several ECM receptor components are increased in PKD patients including various integrins, syndecan-4, as well as the integrin-associated focal adhesion kinase (Geng et al. 1999; Wilson and Burrow 1999; Zeltner et al. 2008; Wallace et al. 2014; Joly et al. 2003). Mitigation of renal cyst formation in response to disruption of these pathways (e.g., by genetic targeting of integrin in mice) points to functional relevance of the cell–ECM interactions in the pathogenesis of PKD (Lee et al. 2015). Of note, a hypomorphic mutation in the laminin alpha5 gene was sufficient to drive renal cyst formation (Shannon et al. 2006).

12.3.3 Fibrotic Cells in PKD

Myofibroblasts are specialized cells that can exert large contractile forces, mediate wound healing, and substantially contribute to the expansion of ECM and development of renal tubulointerstitial fibrosis (Fig. 12.1d) (Qi et al. 2006). A hallmark of myofibroblasts is expression of cytoskeletal alpha smooth muscle actin (αSMA) which is incorporated into stress fibers. While αSMA expressing interstitial cells were found in focal areas during

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early-stage ADPKD, they were found in abundance in end-stage ADPKD kidneys (Hassane et al. 2010). αSMA-positive cells were also found in kidneys from *PKD1*-deficient mice (Hassane et al. 2010) and end-stage PKD kidneys from Han:SPRD-Cy rats (Song et al. 2009; Schieren et al. 2006). Cells expressing high amounts of αSMA are potent producers of ECM proteins including type I and III collagen. Production of excess ECM proteins leads to interstitial fibrosis, tubule and nephron loss, a decline in glomerular filtration rate, and eventual end-stage renal disease. Although the origin of renal PKD myofibroblasts remains unknown, it appears that these cells can differentiate from several different precursors, including resident interstitial fibroblasts, or pericytes (Kuo et al. 1997). Such transformation may be regulated by TGF-β or perhaps by PKD-related alterations in calcium flux (Follonier Castella et al. 2010). Targeting of αSMA-positive cells for anti-fibrotic therapy to help reduce scarring and retain renal function is an attractive idea, although, to date, no such treatment exists.

The origin of myofibroblasts in the kidney of PKD mouse models remains unknown; however, in a UUO model of renal fibrosis, it was shown that a majority of myofibroblasts in the kidney were derived through proliferation of resident fibroblasts although bone marrow-derived fibrocytes also contributed (~35%) to the myofibroblast population (LeBleu et al. 2013). Using fate mapping studies, this group concluded the vascular pericytes likely do not contribute to renal fibrosis. In contrast, Humphreys and colleagues determined that resident pericytes were major contributors to renal myofibroblasts following UUO-induced injury (Humphreys et al. 2010). While the exact reasoning for the discrepancy is unknown, both groups showed that epithelial-to-mesenchymal transition (EMT) was a minor contributor to the SMA+ myofibroblast population following UUO-induced renal injury. Interestingly, EMT may be enhanced in PKD through factors such as TGF-β, platelet-derived growth factor (PDGF), FGF-1, and Insulin-like growth factor (IGF) I and II, all of which are upregulated in cystic disease (Norman 2011; Kuo et al. 1997). Togawa et al. showed that expression of E-cadherin and beta-catenin, components important for epithelial adhesion, was significantly attenuated in tubules from PCK rats (Togawa et al. 2011). Furthermore, cystic epithelial cells found in fibrotic regions showed increased mesenchymal markers including vimentin and fibronectin (Togawa et al. 2011). Gene expression analysis from human ADPKD samples showed significant alterations in the expression of genes related to smooth muscle which led the authors to speculate on a possible EMT in these patients (Schieren et al. 2006). However, a recent study concluded that EMT provides only a minor contribution to the SMA-positive population in PKD kidneys using a *PKD1* mouse model (Hassane et al. 2010). Despite evidence that EMT plays an important role in the formation of myofibroblasts in the kidney (Zeisberg and Neilson 2010), the extent of EMT and its importance for the pathogenesis of cysts and fibrosis in PKD patients is unknown.

The involvement of macrophages in promoting accumulation and degradation of extracellular matrix proteins is well established. Macrophages secrete growth factors and cytokines that induce myofibroblast activation and extracellular matrix production leading to fibrosis (Fig. 12.1d) (Vernon et al. 2010). The most well-defined macrophage-secreted growth factor is TGF-β, which drives extracellular matrix production and fibrosis through binding to the TGF-β receptor present on myofibroblasts (Wynn and Barron 2010). In addition to TGF-β, macrophages are major producers of PDGF and drive extracellular

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matrix production and fibrosis in a bleomycin model of idiopathic pulmonary fibrosis (Bonner 2004). Macrophages also produce other pro-fibrotic growth factors including galectin-3, insulin-like growth factor-I, IL-4, and IL-13, factors that are potent inducers of extracellular matrix production and fibrosis (Wynn and Barron 2010). Specifically, galectin-3 is critical for activation of renal fibroblasts and knockout of galectin-3 reduced fibrosis following unilateral ureteric obstruction (UUO) (Henderson et al. 2008). Despite extensive studies demonstrating that macrophages promote fibrosis, other data indicate that macrophages produce several matrix-degrading proteases including MMP1, MMP2, MMP8, MMP9, and MMP13 and TIMPs (Wynn and Barron 2010). For example, overexpression of MM9 in alveolar macrophages significantly reduced fibrotic lesions and hydroxyproline content compared to controls (Cabrera et al. 2007). Furthermore, adoptive transfer of bone marrow-derived macrophages into leukocyte-depleted mice significantly attenuated fibrosis following UUO-induced injury (Nishida et al. 2005). Collectively, these data suggest that different macrophage subtypes are responsible for promoting or regressing fibrosis through production of matrix promoting or degrading factors although this concept has not been extensively studied in PKD models.

12.3.4 Fibrotic Cytokines and Signaling Pathways

A number of intracellular signaling pathways are activated in cyst-lining epithelial cells in ADPKD, many of which are also activated in fibrosis (Norman 2011). TGF-β, a major fibrogenic cytokine, is highly expressed in cystic epithelia in human, rat, and mouse models of PKD. Studies in rodent models suggest that increased TGF-β expression and signaling correlate with later stages of the disease and that TGF-β is important in cyst progression and fibrosis rather than cyst initiation (Hassane et al. 2010). Activin A is a cytokine that belongs to the TGF-β family of growth factors. During development, activin A is produced by the ureteric bud (UB) and negatively regulates its branching; furthermore, activin A is also involved in kidney regeneration following injury, suggesting an important role for this cytokine during kidney formation/regeneration (Maeshima et al. 2003; Ritvos et al. 1995). More important, inhibition of activin A signaling slows the progression of PKD (Leonhard et al. 2016). Additionally, activin A expression is increased in a *PKD1* mouse, model raising the possibility that altered activin A expression has a role in renal cystic disease (Hassane et al. 2010). Its expression is also associated with conditions wherein loss of cilia or polycystins causes rapid cyst formation (e.g., after injury or in juvenile ages). These studies indicate that activin A is a critical cytokine in cyst progression and ESRD since it is involved in epithelial regeneration and is a member of the TGF-β family of pro-fibrotic growth factors capable of inducing ECM gene expression in renal cells (Yamashita et al. 2004).

In addition to TGF-β, several other pro-fibrotic growth factors were associated with ECM production in PKD including epithelial growth factor (EGF), fibroblast growth factor-1 (FGF-1), and hepatocyte growth factor (HGF). Levels of these pro-fibrotic cytokines increased in PKD over time and their highest levels were often found in end-stage or near-end-stage PKD kidneys (Kuo et al. 1997; Du and Wilson 1995). Furthermore, overexpression of the bone morphogenic protein receptor (ALK-3) or knockout of Bmp-7 triggers cyst formation in mice (Hu et al. 2003; Jena et al. 1997). Importantly, in complementary studies, BMP-7 treatment attenuated renal cystic disease progression in a *jck*

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mouse model of PKD (Leonhard et al. 2016). Similarly, EGF is another important regulator of cystic epithelial cell proliferation and inhibition of this pathway is being targeted for therapeutic development (Du and Wilson 1995). It could be presumed that targeting multiple pro-fibrotic pathways may be an effective means of intervention for patients progressing toward ESRD. Overall, upregulation of multiple pro-fibrotic growth factor components suggests that these cytokines work in conjunction to increase extracellular matrix during PKD progression. However, the specific pathways involved in fibrosis associated with ADPKD remain to be defined.

12.3.5 Anti-Fibrotic Therapies in PKD

Slowing cyst expansion and the development of fibrosis is key to prolonging patient life span and improving palliative care. Although progress has been made (Boor et al. 2007; Fine and Norman 2008; Vilayur and Harris 2009; Albaqumi et al. 2008; Grgic et al. 2009), development of effective anti-fibrotic strategies in PKD patients is very limited. Therefore, it is imperative that we better understand the mechanisms underlying the initiation and progression of fibrosis. Identifying key molecular mechanisms that are impacted during the development of cysts and how they ultimately contribute to ESRD should provide novel targets for anti-fibrotic therapies.

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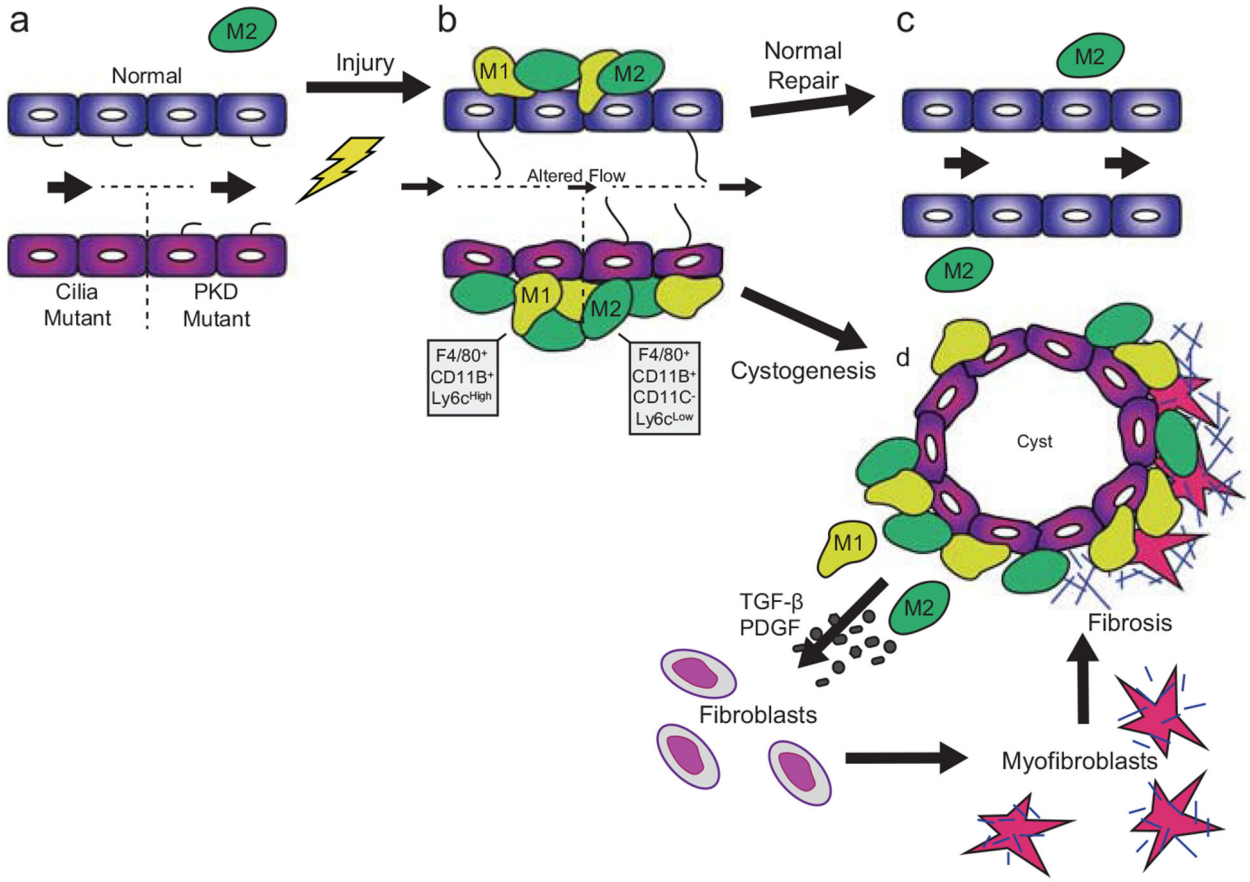

Fig. 12.1.

Proposed model focused on the involvement of macrophages following renal injury under normal conditions and in the presence of ciliary or polycystin dysfunction. (**a**) During steady state, primary cilia protrude into the lumen of renal tubules. Macrophages (M2 like) are present in the interstitial space surrounding the renal tubules. (**b**) Following injury, there is increased accumulation of macrophage populations (M1-like) or (M2-like) in the interstitial space of the kidney. Furthermore, cilia length initially increases following injury followed by cilia regression during stages of rapid epithelial cell proliferation. (**c**) During the repair phase in the normal mouse kidney, the injured tubules proliferate, downregulate inflammatory cell accumulation, reform primary cilia, and fully repair the injured epithelium. (**d**) However, in the cilia or PKD mutant mouse kidney, there is an increased accumulation of macrophage populations (M1 and M2) which fail to properly resolve following injury. The persistent increase in macrophage number leads to enhanced secretion of pro-inflammatory and pro-fibrotic cytokines which causes transition of fibroblasts to a myofibroblast phenotype. These myofibroblasts produce large amounts of extracellular matrix proteins leading to deposition of collagen into the extracellular matrix and fibrosis in the PKD kidney

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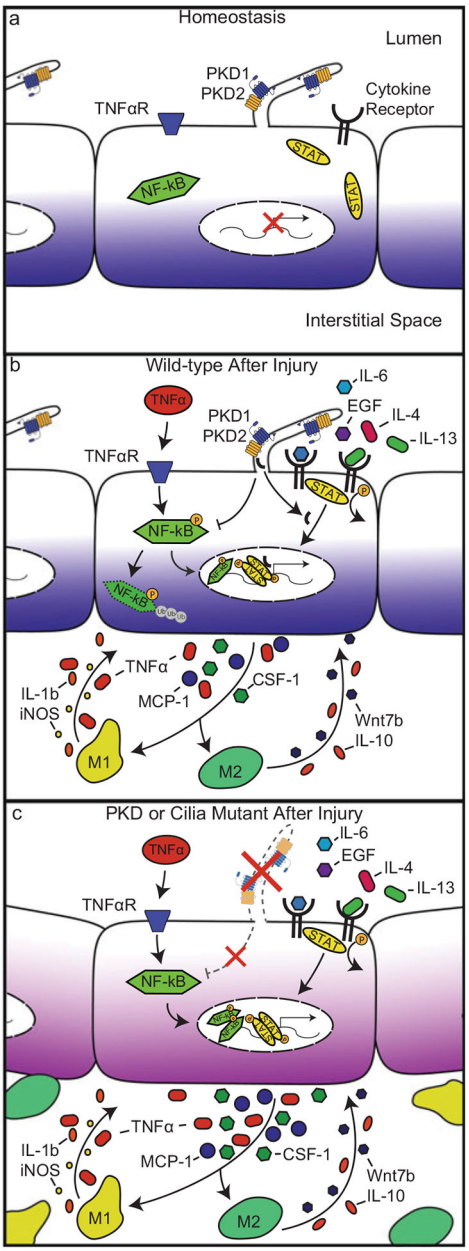

Fig. 12.2.

Inflammatory signaling pathways activated under normal or injured conditions in control, cilia, or PKD mutant epithelial cells. (**a**) During homeostasis, NF-κB and JAK-STAT signaling pathways are not activated. (**b**) In injured wild-type epithelial cells, PC1 undergoes C-terminal tail (CTT) proteolytic cleavage. The CTT of PC1 translocates into the nucleus where it serves as a co-activator of the STAT signaling pathway. The NF-κB pathway is also activated through ligands, such as TNF-α, binding to their cognate receptors on the cell surface. Collectively, activation of the NF-κB and JAK-STAT signaling pathways induces transient activation of pro-inflammatory genes such as MCP-1, TNF-α, and CSF-1. These cytokines rapidly recruit macrophages to the site of injury leading to production of pro-inflammatory (IL-1β, TNF-α, iNOS) and anti-inflammatory cytokines (IL-10, Wnt7b) that

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feed back to the injured epithelium leading to tissue repair. (**c**) In injured PKD or cilia mutant epithelial cells, there is persistently increased NF-κB and JAK-STAT pathway activation. The persistent activation of NF-κB and JAK-STAT signaling leads to enhanced production of pro-inflammatory, pro-fibrotic, and chemoattractant cytokines and increased macrophage accumulation. Accumulated macrophages produce cystogenic cytokines such as TNF-α or Wnt7b that may be responsible for driving cyst formation