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Research Paper

Polycystic Kidney Disease: A Paradigm in Major Kidney Disorders

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The normal architecture of the kidney is crucial for maintaining biological function and its homeostasis. Its proper development depends on highly dynamic processes which modulate the integrity of its associated cellular functions, interactive events and regulatory cascades that altogether provide proper turnover in adult life. Any alteration in regulatory processes and normal utility holds crucial consequences for proper functioning of the kidney. These variations accompany renal injury, various etiologic events, deviation from genetic-wild type processes and metabolic disturbances leading to major lesion of end-stage renal disease (ESRD). Major renal disorders developing today and affecting millions of people globally include diabetes, hypertension, glomerulonephritis and Polycystic Kidney Disease (PKD). Among these diseases, PKD is becoming relatively common, and has emerged as one of the largest causes of renal transplantation and dialysis. Therefore, understanding the development, function and progression of normal kidneys *vis a vis* cystic renal kidneys serves an important way in understanding pathophysiology of PKD and cystogenesis.

Keywords: Kidney; Polycystic Kidney Disease; End-Stage Renal Disease; Polycystin-1; Polycystin-2

Introduction

The normal architecture of the kidney is crucial for maintaining biological function and its homeostasis. Its proper development depends on highly dynamic processes which modulate the integrity of its associated cellular functions, interactive events and regulatory cascades altogether providing proper turnover in adult life. Any alteration in regulatory processes and normal utility holds crucial consequences for proper functioning of the kidney. These variations accompany renal injury, various etiologic events, deviation from genetic-wild type processes and metabolic disturbances leading to major lesion of ESRD. Major renal disorders developing today affecting millions globally include diabetes, hypertension, glomerulonephritis and PKD. Among these diseases, PKD is becoming relatively common, and has emerged as one of the largest causes of renal transplantation and dialysis. Therefore, understanding the development, function and progression of normal kidneys to cystic renal kidneys serves an important way in understanding pathophysiology of PKD and cystogenesis.

Kidney and Its Organogenesis

The kidney is a widely used model to study the systematic approaches toward intricacies of tissue development and vertebrate organogenesis. The mammalian kidney, or also known as the metanephros, arises at ~35th day of human gestation period. The events involved in kidney development were elucidated by manoeuvring the amphibian, avian and mammalian embryos through *in vitro* organ cultures. Permanent kidney establishment takes place by two fundamental processes (i) nephronogenesis and (ii) branching morphogenesis. Kidney starts developing from primordial mesodermal derivatives, andits induction begins when signals are sent by the ureter upon which the metanephric mesenchyme starts condensing around the ureteric bud (Lechner *et al.,* 1997; Bjelakovic *et al*., 2018). The pronephros is composed of a single glomus, and projects into the nephrocoel filtering directly into the coelom. The mesonephros consists of multiple nephrons that develop in a cranial to caudal fashion. The metanephros at this stage comprises the ureteric bud, which enters the metanephric mesenchyme. The

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condensed metanephric mesenchyme evolves into tubular epithelium of mature nephron. Once nephrogenesis begins, it leads to the formation of glomerulus and all tubules except the collecting ducts, and segments into glomerular and tubular domains by forming two clefts in renal vesicles (Kopan *et al*., 2007).

Collecting ducts, on the other hand, form by branching morphogenesis along with the calyces, renal pelvis and ureter bud (Saxén 1987; Yamashita and Nishinakamura, 2005). The ureter bud originates from the epithelial outgrowth of the caudal portion of the Wolffian ducthence, giving rise to the renal collecting system. By 20-22 weeks' gestation period, completion of ureteric branches takes place followed by the collecting duct development. By 22-44 human fetal gestation, cortical and medullary domains of the developing kidneys are established. The renal cortex by birth represents 7% of the total kidney volume (Cebrián *et al.,* 2004). Convergence of the collecting ducts in the inner medulla form papilla, which give rise to distinct morphological differences between medullary collecting ducts and those of the renal medulla. Once the inner mass and proper morphology of kidney develops, the full complement of glomerulus takes place by 32-34 weeks when nephrogenesis ceases. At birth the last glomeruli to be formed is the superficial glomeruli. Finally, by 3.5 years of age subsequent glomeruli development involves hypertrophy (Dressler 2006; Fetterman *et al.,* 1965; Rosenblum 2008).

The attainment of proper morphological kidney for its correct functioning involves complex processes, which derive gene expression of renal cells to properly regulate homeostasis at molecular level. Early developmental stages of the kidney are rich in expression of various genes, and its proteins are highly expressed to regulate cellular proliferation and differentiation. Any mismatches in these genetically controlled programs, either hereditary or somatic, may lead to altered morphology or improper functioning of the kidneys.

Genetic Programs and Transcription Factors Controlling Kidney Development

Genetic programs during developmental stage of an organism play a decisive role in turning a particular cell type into a proper functioning tissue. Many of these genetically controlled programs also operate during early embryonic kidney development, and these potential signalling molecules affect its morphogenesis. The 'master regulators' set up a basic pattern formation of specific differentiation programs such as nephron development, mesenchyme differentiation or ureteric bud development.

In the initial stages of kidney development, nephrons, ureteric bud branches,metanephric andmesechymal (stromal) cells themselves contribute towards normal kidney development (Cullen-McEwen *et al.,* 2005). The expression pattern is controlled by *forkhead boxd1* (Foxd1), *r*etin*al*dehyde *deh*ydrogenase *2* (Raldh2), *r*etinoic *a*cid *r*eceptor *a*lpha (Rara) and –beta (Rarb2) along with *f*ibroblast *g*rowth *f*actor-*7* (Fgf7), *pod*ocyte-*1* (Pod1) and Bmp4. Another family of Pax genes encode evolutionary conserved transcription factors important in proceeding nephrogenesis in stepwise manner (Eccles *et al.,* 1995; Gruss and Walther 1992; Torres *et al.,* 1995). Along with other Wnt gene family, Wnt4 and BM7 are also known as important regulators of nephron maturation and many other morphogenic events (Lyons *et al.,* 1995) required for proliferation and differentiation. p53 and Hox genes expressed in the developing kidneys regulate cell cycle, apoptosis and specifying positional information and anterior posterior axis, respectively (Krumlauf 1994).

Any mutation or altered expression of the specific underlying genes may lead to severe form of renal disease. Renal mutation analyses in mice and human have yielded a great insight into the genes involved and their role in controlling kidney development. Expression of these genes has not only provided an insight into the transcriptional mechanisms, but molecular pathways have also been identified, which in turn have helped carry out further work on understanding kidney defects and diseases.

Polycystic Kidney Disease: Facts and Pathogenesis

Historical references to PKD can be found to be dated as early as 15th century when King of Transylvania died at the age of 53 years. His kidneys were found to have humongous size and "bumpy" surface. No reference on study of PKD existed till 1899 when its genetic basis was first suggested by Steiner, but understanding the genetic abnormalities underlying

PKD took almost another 100 years of research to unravel the mechanistic approaches by which the disease had become extremely prevalent. In the middle of the 20th century, comprehensive study describing the disease and its inheritance as an autosomal dominant trait was published by Dr. O. Z. Dalgaard in 1957, and throughout the years of extensive research PKD was established as a systemic heterogenetic life-threatening disorder among all racial groups. Today, approximately 12.5 million people are affected worldwide (Tan *et al.,* 2011) including 2.3 million Indians alone (Modi and Jha 2006).

Heterogeneous group of cystic diseases are renal inherited conditions, which involve 33 genes covering X-linked autosomal dominant and autosomal recessive inheritance showing Mendelian inheritance (Deltas and Papagregoriou 2010), but cyst development and characterization of PKD is not properly understood. The cysts start as focal entities from dedifferentiated tubular epithelial cells forming single cell lining (Qian *et al.,* 1996). As the disease progresses, formation of extra-cellular matrix is accompanied by slow and progressive cyst enlargement disturbing the normal parenchyma and renal architecture. Disease progression leads to enlargement of kidneys four to six times its normal size. PKD being highly heterogeneous, its symptoms may vary according to individuals and their lifestyles (Martinez and Grantham 1995). Frequent symptoms that affect majority of the individuals include kidney stones, urinary tract infections, hypertension, and severe abdominal pains. Although the name describes renal disorder, but the disease is systematic, and includes numerous cystic and non-cystic extrarenal manifestations. Cystic outgrowths are limited not only to kidneys, but liver, seminal vesicles, pancreas, spleen and thyroid also get affected. (Hossak *et al.,* 1988; Pirson *et al.,* 2002). Abnormalities in other organ functions gradually develop with time and patients suffer from cardiac valve defects, intracranial and aortic aneurysms, inguinal hernia and colonic diverticula especially in PKD patients (Demetriou *et al.,* 2000, Gabow 1993; Gieteling *et al.,* 1993; Scheff *et al.,* 1980; Torra *et al.,* 2008; Wiebers *et al.,* 2003). Disrupted cell functions, aberrant renal epithelial organization and decline in nephron functioning takes placeduring renal transplantation and ESRDand hence,conferring patients with life expectancy of 53-60 years.

PKD Phenotypes

PKD inherited disorders are mainly characterized by the progression and severity of symptoms related to the type of variability. Three major forms of PKD are: (a) the common, late onset-autosomal dominant polycystic kidney disease (ADPKD); (b) the mainly infantile-autosomal recessive polycystic kidney disease (ARPKD); and (c) the lethal-syndromic, Meckel syndrome, characterized by renal cystic dysplasia.

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is an inherited disorder effecting the newborns and younger patient population (Capisonda *et al.,* 2003; Guay-Woodford and Desmond 2003) with an estimated incidence of approximately 1:20,000 live births (Zerres *et al.,* 1998). Often the newborns are either stillborn or born with massively enlarged, cystic kidneys, and die in the perinatal period from respiratory failure. These cystic kidneys retain their reniform shape, but cysts are presented with increased cell proliferation, fluid secretion, cystic dilations mainly of the collecting ducts, dysgenesis of the biliary ductal plate and congenital hepatic fibrosis, altogether, resulting in death at the perinatal stage (Kaimori and Germino 2008). The kidneys are often bilaterally enlarged, multicystic depicting abnormal proliferation, differentiation and epithelial polarity defects (Woo 1995).

The linkage to ARPKD has been traced to6p21.1-p12 caused by single gene mutation in the polycystic kidney and hepatic disease 1 (*PKHD1*) (Mücher *et al.,* 1994). Being among the largest human genes with minimum 86 exons having alternatively spliced variants, it is highly expressed in kidney with lower levels seen in liver and pancreas. The longest and continuous open reading frame (ORF) yields 4,074 a.a (447 kDa) receptor-like integral membrane protein (fibrocystin/polyductin) containing multiple copies of an Ig-like domain (TIG) (Bergmann *et al.,* 2004; Boletta *et al.,* 2001; Onuchic *et al.,* 2002; Ward *et al.,* 2003). It is mainlylocalized to the branching ureteric bud; collecting and biliary ducts; and the ascending limb of Henle's loop, but seen to be often absent from ARPKD. Screens of *PKHD1* have revealed over 119 different mutations spread throughout the gene. Majority of the patients screened

are compound heterozygotes having two truncating mutations with severe disease onset tissue (Harris and Rossetti 2004). Fibrocystin is found to be localized in the axoneme and primary cilia of renal epithelial cells supporting the link between ciliary dysfunction and cyst development hence, reinforcing a link with the PKD-related proteins (Harris and Rossetti, 2004; Landis *et al*., 2018).

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Massive enlargement of kidneys with number of large cysts is hallmark of ADPKD afflicting approximately 1 in 1,000 individuals (Grantham 2008; Paterson *et al.,* 2005; Wilson 2004). Roughly 50% of the patients with ADPKD require renal replacement therapy by the age of 60 years (Torra 2008). Cysts in ADPKD tremendously increase in size over a decade, displacing and destroying the three-dimension (3D) organ structure of the kidney by annihilating the normal renal parenchyma, andseverely compromising its functional integrity. Cyst formation starts at an early stage and continues throughout the entire life of the affected individual ultimately resulting into ESRD. Although the magnitude of cellular de-differentiation and apoptosisis a consequence of small genetic dysregulation, but it gives rise to multiple renal cysts mainly derived from proximal and distal tubules and collecting ducts; and hence originate from less than 1% of the nephrons cystsremains connected to the nephron of origin (Baert 1978; Li 2011; Mochizuki 2013; Shibazaki *et al.,* 2008). Dilations in the tubules from an early staged ADPKD patient show thickened and deformed basement membrane having single layer of lined epithelial cellswith abnormal proliferation, protein sorting defects and altered planar cell polarity (Fick 1995; Happé *et al.,* 2011; Milutinovic *et al.,* 1980).

Many factors associated with the variability of the disease such as hypertension, early onset, male gender, increase in kidney size and growth rate of cysts in multiple organs, and microalbuminuria are said to contribute towards progression of the disease (Boucher and Sandford 2004; Fick *et al.,* 2001; Grantham 2006; Schrier *et al.,* 2003). Patients experience pangs of abdominal pain, hypertension, renal insufficiency, hematuria and/or proteinuria (Torres *et al.,* 2007). Renal functioning begins to decline in the fourth decade of life especially males experiencing faster decline in GFR (*glomerular filtration rate*) than females (Grantham *et al.,* 2008). GFR decreases by 4.4 to 5.9 L/min per year being inversely proportional to kidney size and cyst volume grossly varying from the normal (Grantham *et al.,* 2006; King *et al.,* 2003; Li, 2011; Torres and Harris 2009). Its progression and risk factors have been the prime targets, but in all cases evidence leads to large renal volume associated with decreased renal blood flow (Grantham 2008). Patient mortality is accredited to these extra renal manifestations, and each patient has his own signature of cyst growth that shows highly variable age of onset and clinical course (Churchill *et al.,* 1984; Franz and Reubi 1983; Reeders *et al.,* 1985). Although cyst growth is slow and progressive, it develops throughout the life of a patient hence, limiting the life of a patient to an average of 54.3 years (Hateboer *et al.,* 1999).

Genetics Defining ADPKD

ADPKD Genes: PKD1 and PKD2

Linkage analysis has revealed at least three forms of ADPKD genes causing clinical presentations-*PKD1* (Hughes *et al.,* 1995; Reeders *et al.,* 1985), *PKD2* (Kimberling *et al.,* 1993) and*PKD3* (Daoust *et al.,* 1995). *PKD1* gene located on human chromosome 16p13.3 encodes a 14 kb mRNA that is spliced from 46 exons extending over ~50 kb of DNA translated intoprotein product polycystin-1 (PC-1). The *PKD1* region is complex, with 5' region of the gene being composed up to exon 33, and repeated several times more proximal on chromosome 16 (Consortium 1996; Harris 1999). The other gene form *PKD2* on human chromosome 4q21-23 spanning 15 exons encodes polycystin-2 (PC-2) (Hughes *et al.,* 1995; Mochizuki *et al.,* 1996; Lanktree and Chapman, 2017). Both genes involve loss of function mutations, deletion, frameshifts or nonsense mutations however, approximately 85% of the cases are attributable to *PKD1* gene mutations, while *PKD2* accounts for the remaining (~15%).

PKD Proteins: Polycystin-1 and Polycystin-2

Polycystin-1(PC-1)

PC-1 is a 4302 a.a (462 kDa) integral plasma membrane non-tyrosine-kinase receptor with a large

extracellular NH_2 terminal domain (3074 a.a with multiple binding domains), 11 transmembrane domains (1032 a.a.) and short COOH terminus (~222 a.a). It is found in the basolateral plasma membrane domain of polarized epithelial cells participating in cell-cell or cell-matrix interactions (Wilson and Falkenstein 1995). The NH_2-terminal domain, involved in protein-protein and protein-carbohydrate interactions (Nims *et al*., 2003), contains distinct combination of recognized motifs including: two leucine-rich repeats, a C-type lectin, sixteen copies of PKD domain, a region of homology with a sea urchin protein-the receptor for egg jelly (SUREJ) (Moy *et al.,* 1996) required for triggering transmembrane cation influxes of Ca^{2+} ions for acrosome reaction (Trimmer *et al.,* 1985) and a GPCR proteolytic site (GPS domain) (Ponting *et al.,* 1999) suggesting that these unique regions of the protein may also play a role in regulating ion transport. One of the defining features of PC-1 is its homology with lipo-oxygenase (polycystin/lipo-oxygenase/á-toxin pr PLAT) domain embedded in the first cytoplasmic loop of PC-1. This suggests that PC-1 extends its interactions with other proteins. The regions REJ, GPS and PLAT domains, therefore, mark a defining feature of the protein. The COOH-terminus holds a G-protein binding and activation domain (Qian *et al.,* 1997), phosphorylation sites and coiled coil domain required for interaction with COOH terminal of PC-2 (Parnell *et al.,* 1998), including sequence that is rich in proline, glutamic acid, serine and threonine (PEST) are facilitating its ubiquitin-mediated degradation (Low *et al.,* 2006; Rechsteiner and Rogers 1996).

A cleavage product of PC-1, the C-terminal tail, can translocate to the nucleus and regulate gene transcriptionregulating epithelial cell growth, migration, differentiation, cell cycle and apoptosis (Bhunia *et al.,* 2002; Manzati *et al.,* 2005; Nickel *et al.,* 2002;Yu *et al.,* 2011).

Polycystin-2 (PC-2)

PC-2 has been identified as a distant member sharing homology with the *t*ransient *r*eceptor *p*otential family of ion channel (TRP) spanning six transmembrane domains with intracellular N and C termini (Chen 1999; Koulen *et al.,* 2002; Mochizuki *et al.,* 1996). PC-2 functions as a Ca^{2+} permeable non-selective cation channel that transports and modulates intracellular Ca^{2+}, and releases calcium from intracellular stores in accordance with changes in local concentration (Vassilev *et al.,* 2001). Several domains present in the PC-2s' N- and C- terminals contribute to its protein-protein interaction and Ca^{2+}sensitivity with EF hand domain having single Ca^{2+} binding domain permitting protein to sense $Ca^{2+}$and buffer changes. This domain ensures its localization to its subcellular maintenance to ER and Golgi. Having control over local Ca^{2+} changes, cytoplasmic calcium levels are also indirectly regulated by PC-2 through interactions with two major intracellular Ca^{2+} channels: the ryanodine receptor and the *i*nositol 1,4,5-tris*p*hosphate *r*eceptor (IP3R) (Anyatonwu *et al.,* 2007; Di Mise *et al.,* 2018; Kim *et al*., 2000).

Both PC-1 and PC-2 when localized to the primary cilium form a complex, which has a mechano-sensory role in translating mechanical and chemical stimuli of Ca^{2+} around inter- and intracellular responses. Cells showing *PKD1* mutation fail to maintain calcium levels due to dysfunctional cilia.

Expression Patterns and Interaction of PC-1 and PC-2

Epithelial cells of the developing renal tissue show highest expression of PC-1 with mature renal tubules expressing lower,but detectable levels as well as other somatic tissues including heart, liver, bone, brain, bowel, placenta, thymus endocrine glands and endothelium arteries and veins (Ibraghimov-Beskrovnaya *et al.,* 1997; Markowitz *et al.,* 1999; Ong *et al.,* 1999; Ward *et al.,* 1996) with PC-2 localizing to the subcellular compartments of the ER along with PC-1 and early Golgi (Cai *et al.,* 1999; Koulen *et al.,* 2002). Maximum levels of PC-1 can be found in the fetal renal tissue with low levels present in adults (Chauvet *et al.,* 2002). PC-1 and -2 arelocalized mainly in the cilium, but also found in the lateral domain of polarized renal epithelial cells (Huan and van Adelsberg 1999; Yoder *et al.,* 2002), with PC-2 also seen residing in centrosome and mitotic spindles (Rundle *et al.,* 2004). Collecting ducts are enriched in PC-1 and PC-2 dominating in the medullary thick ascending limb and distal cortical tubules (Foggensteiner *et al.,* 2000) with their expressions higher during developmental stages as shown in animal studies. Mouse development as early as E9.5-E12.5 show highest levels of these proteins in mesoderm

and ectoderm (Guillaume *et al.,* 1999) with PC-1 detected significantly at E17.5 in the kidney in branching ureteric buds, tubules and Bowman's capsules (van Adelsberg *et al.,* 1997; Weston *et al.,* 2003). Hence, this mutual subcellular localization of PC-1 and PC-2 explain their working in concert with each other in regulating kidney homeostasis.

The interactions of both PC-1 and -2 participate in fluid flow sensing through ciliary bending and kidney pressure (Patel and Honoré, 2010; Praetorious and Spring 2003), and are functionally co-dependent. Their strong co-localization in the primary cilium and ER suggests that their give-and-take interactions affect each other's surface membrane and ciliary localizations impairing the function of one protein and affecting the nature of the other protein. Communication of both proteins is important in creating functional ion channel. A physical interaction of PC-1 and PC -2 occurs through their C-terminal cytoplasmic tail (Casuscelli *et al.,* 2009; Tsiokas *et al.,* 1997). The protein-protein mediated interaction is carried by specific tyrosine or serine targeted phosphorylation and proline rich SH3 sites (Li *et al.,* 2004). This interaction not only carries functional stability for ion movement, but their inability to interact decreases PC-1's ability to activate G-proteins and leading to cyst formation in ADPKD (Delmas*et al.,* 2002). Depending on their interaction many pathways have been identified which activate and control normal functioning of *PKD1* gene regulation by various transcriptional mechanism or activated through downstream signalling pathways.

ADPKD and Pathogenesis

The interaction of PC-1 and PC -2 leads to microenvironment changes in cell-cell, cell-matrix biology and intracellular mechanism. Any perturbation in their cross-talks effecting downstream signalling leads to ADPKD pathogenesis hence, culminating to renal cystogenesis and cystic lesions.Often these amended mechanisms cause cyst initiation and formation and are the key factors in targeting cyst growth and progression of the disease.

Molecular Mechanism of Cyst Formation and Fluid Secretion in ADPKD

Cyst formation mechanism shows variable pathways in cyst initiation and formation. ADPKD patients who have inherited one mutated copy of *PKD1* will develop and function normally into adulthood having only the "first hit". However, if over the year's cyst formation takes place in the patient's kidneys, the cysts will have lost both the functional copies of this gene (Brasier and Henske 1997; Qian *et al.,* 1996; Halvorson *et al.,* 2010; Messchendorp *et al*., 2018). The "second hit" somatic mutation knocks out the normal *PKD1* or *PKD2* allele resulting into cells devoid of a functional allele causing cysts to form through uncontrolled proliferation of cells having two hits. This mechanism of cyst formation is a consequence of distinct somatic mutation event which contributes towards slow progression of the disease over the decades. Total inactivation of PC-1 and PC-2 in the kidneys of mice models has revealed severe cystic disease during the developing stages rather than complete loss of PC-1 and PC-2 in mature kidneys (Lantinga-van Leeuwen *et al.,* 2007; Piontek *et al.,* 2007). *PKD1* knockout in adult mice kidneys causes similar phenotype (Takakura *et al.,* 2008) suggesting that injury may be sufficient in cyst formation in heterozygotes without requiring the "second hit"

Table 1: Summary of ADPKD Genes and Protein Characteristics (Gallagher *et al.,* 2010)

	PKD1	PKD2
Mutations in ADPKD families	85%	15%
Mean age of onset ESRD	53 years	69 years
Gene Characteristics	Ch16q13.343 exons gene size, ~46 kb	Ch4q21-23, 15 exon gene size, ~3.5 kb
Protein Characteristics	PC-1, 4302 a.a, 11transmembrane domains receptor- like proteinundergoes proteolytic cleavage	PC-2, 968 a.a, 6 transmembrane domains, Homology to TRP channels
Subcellular localization	Cilia, cell junctions, apicaland basolateral plasma membrane	Cilia, endoplasmic reticulum, plasma membrane
Function	Receptor	Cation channels

mutagenesis. This mechanism suggests that somatic mutation is either allowing transcription of the mutated wild-type allele or blocking production of PC-1 and PC-2. Once the normal functional genes are inactivated, it gives way to abnormal focal proliferation of renal tubular cells, mitotic orientation defects and disruption of fluid flow sensitivity (Nauli *et al.,* 2003; 2006).

Cells losing fluid flow-sensitivity leads to increased surface area of cyst wall and fluid secretion filling the cavity, and hence increasing the number of cells surrounding the cysts' lumen (Grantham 1987). Renal cyst formation is mild in adult mice heterozygote for *PKD1* and *PKD2* mutations, but mice homozygous embryos possess severe cyst expansion from E15.5 day onwards.

Even though complete knockout of *PKD1*and *PKD2* causes massive cyst formation, another hypothesis proposed towards cystogenesis is the "*gene dose effect*". This hypothesis explains complete absence, haploin sufficiency or transgenic over expression to be the basis of cyst formation (Koptides *et al.,* 2000; Lantinga-van Leeuwen*et al.,* 2004; Lu *et al.,* 1999; Pritchard *et al.,* 2000). Therefore, the development and growth of cyst requires a net influx of fluids converting the normal epithelium to cystic secretory epithelium. This transformation is predicted involving: cells organizing themselves into spherical rather than tubular structures, and filling of these lumens with fluid to expand into cysts. Increase in the cyst surface area is not due to stretching of the epithelial cells, but rather due to cells dividing unconditionally surrounding the cyst lumen (Chapin and Caplan 2010). Expansion of these cystic epithelium experience abnormal cell proliferation and apoptotic loss of nephrons and epithelial cells (Koupepidou *et al.,* 2010; Woo 1995).

Table 1: Studies evaluated for detailed analysis for at risk CVD patients for inflammatory and LAM biomarkers and basic variables

S. No.	Author (s)	Year
1	Kim *et al.*	2009
2	Ridker*et al.*	1997
3	Vasan*et al.*	2001
4	Costello *et al.*	2016
5	Pai*et al.*	2004
6	Roger *et al.*	2007
7	Kurian *et al.*	2007

Microdissection and monolayer culture of the cystic ADPKD epithelia also exhibited fluid secretion,which can be induced by initial fluid formation or activation of the adenylate cyclase signal transduction pathway by cAMP (Grantham *et al.,* 1995; Sullivan and Grantham 1996). Many studies have targeted various modulators implicated in fluid secretion mechanism. One study showed mislocalization of Na,K-ATPase to the basolateral cell surfaces (Carone *et al.,* 1994) in *m*urine *c*ystic *k*idneys (*mck*), and its persistence in cystic collecting tubules (Avner *et al.,* 1992). Other critical aspect of cyst formation is likely to be alteration in orientation of cystic tubules (Nishio *et al.,* 2010) leading to defects in planar cell polarity. These ion-secretory epithelia derive the paracellular or trans-cellular osmotic water movement into the cyst lumen having Cl^- as the prime component in the secretion stimulated by cAMP involving apical *c*ystic *f*ibrosis *t*ransmembrane *r*egulator (CFTR) (Davidow *et al.,* 1996). CFTR has been found to be expressed on the apical cell surface of cystic cells (Hanaoka *et al.,* 1996). Cultured MDCK cells expressing full- length PC-1 with CFTR showed decreased surface localization of CFTR and cAMP stimulated activity (Ikeda *et al.,* 2006) suggesting PC-1 misregulation may lead to increase in CFTR activity.

Cilia and ADPKD

Primary cilium is a hair-like structure rooted to the centriole projecting through the cell and involved in mechanical-sensation function. Experimental evidence has shown cilia bending to be triggered by fluid flow leading to increase in intracellular bending (Praetorius and Spring 2003), and playa central role in ADPKD pathogenesis. Mutational analysis of *i*ntraflagellar *t*ransport *g*ene (IFT) required for maintenance of cilia structure has been associated with PKD development (Lehman *et al.,* 2008; Mohieldin *et al.,* 2015).

Localization of PC-1 and PC-2 in primary cilia of renal epithelium cells shows a strong co-relation of these factors in coordinating cellular response to changes in fluid flow mechanism in normal and renal cystic cells. Working as flow sensors and eliciting calcium transients due to response in bending involves role of PC-1 and PC-2 (Kotsis *et al.,* 2013). Further

Table 2: Biomarkers and basic variables studied and their abbreviations

Inflammatory	
P-Selectin	TNFRI
E-selection	IL-18, interleukin 18
CRP, C -reactive protein	MCP-1, monocyte chemotactic protein-1
SAA, serum amyloid A	RANGE, receptor for advanced glycationendproducts
TIMP-1/2, tissue inhibitor of metalloproteinases-2	Hsp27, heat shock protein 27
ICAM, intercellular adhesion molecule	MMP-2/9, matrix metalloproteinase
VCAM, vascular cell adhesion	ApoA/B/E, apolipoprotein B
MPO, myeloperoxidase	LDL, low-density lipoprotein
Basic Variables	
Age, years	Smokers, %
BMI, kg/m^2	Previous history of MI or stroke (PH)
Total cholesterol, mg/dl	Statin usage, %
HDL cholesterol, md/dl	Aspirin usage %
Systolic BP, mm Hg	Physical activity, %
Diastolic BP, mm Hg	Alcohol (oz)/month

support came from inactivating *K*inesin *f*amily *m*ember 3a (KIF3a), a component of the kinesin-2 motor complex required for cilia maintenance in the kidney which resulted in cyst formation (Lin *et al.,* 2003).

Animal Models of PKD

Studies conducted using PKD experimental models have elucidated various mechanisms towards renal cyst formation, and its underlying pathophysiology. These models have immensely contributed towards studying the basis of pathophysiology of PKD hence, revealing an insight into possible molecular based disease outcomes, endogenous/exogenous athways related to disease progression and targeting possible therapeutic novelties in consideration to means operating in humans.

Spontaneous hereditary models of PKD possess symptoms of human PKD phenotype. One of the models developed was *Han-SPRD-cy* rat in which numerous renal cysts were caused by a missense mutation (C to T, R823W) in exon 13 of *PKDR1* gene on rat chromosome 5. Renal cysts were observed in both homo- and heterozygous rats (Kaspareit-Rittinghausen *et al*., 1989). PCK rats were initially derived from *S*prague-*D*awley (SD) outbreeding colony. In this rat, *PKHD1* gene, an orthologous gene affectedin human ARPKD patients, resulted in cystic kidneys and liver by frameshift mutation in exon 36 (Katsuyama *et al.,* 2000). Many mice models such as *cpk*, *pcy*and *jck* also possessed single point mutations resembling ADPKD characteristics (Atala *et al.,* 1993; Hou *et al.*, 2002; Lu *et al.*, 1997; Omori *et al.,* 2006). Despite having spontaneous mutation in various strains leading to PKD phenotype, gene-modified models such as transgenic mouse models offered controlled expression of human orthologous *PKD1* gene. Transgenic mice models with $PKD1^{-/-}$, $PKD1^{del2\text{-}6/+}$, $PKD2^{WS25-}$ showed complete loss of renal function and severe cystic phenotype, haploinsufficiency, increased apoptosis, respectively. These models further helped target signaling pathways coherent with the human ADPKD (Takahashi *et al.,* 1991). All models developed were specific in targeting various signaling pathways such as mTOR, MAPK, ERK and STAT3, which are important in implication of PKD cystogenesis (Nagao *et al.,* 2012).

Signaling Crosstalk and Transcription Factors in PKD

Polycystin proteins modulate diverse signaling pathways and their downstream targets with hundreds of proteins interacting directly or indirectly with the polycystins (Yang *et al.,* 2008). Many of these signal

Table 3: Differences of biomarkers based on sex and ethnicity of the circulating biomarkers (Kim *et al*., 2010)

	Women (n=1638)			Men (n=923)		
	AA (n=936)	NHW (n=702)	p	AA (n=388)	NHW (n=535)	p
Inflammation						
CRP, mg/L	3.59***	3.33***	0.1528	2.91	2.1	<.0001
SAA, µg/mL	22.63***	22.77***	0.9013	16.91	15.94	0.3587
ICAM, ng/mL	274.48*	284.74	0.0334	260.41	279.91	0.0015
VCAM, ng/mL	570.21	687.62	<.0001	558.63	670.71	<.0001
IL-6, pg/mL	7.98	7.3	0.0053	7.9	7.78	0.7422
IL-18, pg/mL	60.49	69.58**	<.0001	61.58	75.7	<.0001
TNFRI, pg/mL	1027.66	1266.95	<.0001	1046.58	1302.81	<.0001
TNFRII, pg/mL	1731.16	1857.16	0.0012	1751.27	1889.1	0.0029
MCP-1, pg/mL	978.56	859.33*	<.0001	980.77	901.42	0.0012
E-selectin, ng/mL	68.85	69.36	0.6689	70.69	72.19	0.3334
P-selectin, ng/mL	30.09**	27.66***	0.0016	32.8	32.87	0.9512
Hsp27, ng/mL	1726.27	1484.84**	0.0041	1721.46	1274.73	<.0001
MPO, ng/mL	36.56	28.54**	<.0001	34.7	25.08	<.0001
RAGE, pg/mL	437.96***	597.53	<.0001	359.32	560.34	<.0001
MMP-2, ng/mL	1807.08	1693.05	0.0015	1808.72	1705.78	0.0142
MMP-9, ng/mL	29.18	34.66	<.0001	30.01	36.16	<.0001
TIMP-1, ng/mL	68.47***	83.92***	<.0001	75.18	92.97	<.0001
TIMP-2, ng/mL	156.29	148.24	0.0013	152.29	146.87	0.0556
Lipoprotein metabolism						
ApoA-I, mg/dL	164.85***	169.53***	0.0358	137.75	139.3	0.515
ApoB, mg/dL	92.22	97.61	0.0001	89.77	97.96	<.0001
ApoC-III,mg/dL	14.02***	18.19***	<.0001	12.98	16.32	<.0001
ApoE, mg/dL	5.26***	5.14***	0.2681	4.68	4.79	0.3739
LDL size, nm	269.34***	270.60***	<.0001	267.89	269.28	<.0001
Lp(A), mg/dL	46.83***	15.76*	<.0001	35.8	13.85	<.0001
Ox-LDL, U/L	62.31	65.59	0.0024	63.48	65.94	0.0882
Lp-PLA, mass, ng/mL	204.34*	242.36**	<.0001	211.39	253.29	<.0001
Lp-PLA, activity, ng/mL	119.30***	129.67***	<.0001	137.11	154.89	<.0001
Adiopocyte metabolism						
Leptin, mg/mL	26.51***	22.46***	<.0001	9.62	8.81	0.0337
Adiponectin, µg/mL	10.11***	13.07***	<.0001	7.62	9.56	<.0001
Resistin, ng/mL	3.62**	3.76***	0.1519	3.24	3.39	0.1975

transduction pathways are associated with either cilial function or carry out independent pathways. Perturbations in any of these strictly regulated pathways lead to alteration in transcriptional dysregulation, cellular proliferation and apoptosis which culminates into cyst formation.

One of the main pathways studied is the direct interaction of PC-1 and PC-2 and their downstream targets through regulation of intracellular levels of Ca^{2+} and cAMP accumulation during cystic growth. Alteration in this pathway further exasperates Ras/RAF/ERK activation (Arnould *et al.,* 1998;

Table 4: Base variables considered based on sex and ethnicity (Kim *et al*., 2010)

	Women (n=1638)			Men (n=923)		
	AA (n=936)	NHW (n=702)	p	AA (n=388)	NHW (n=535)	p
Age, Years	63.3±9.4	58.4±10.3	<.0001	64.3±9.0	59.5±10.0	<.0001
BMI, Kg/m²	32.5±7.0	30.8±7.1	<.0001	29.2±4.9	30.7±5.1	<.0001
Total Cholesterol, mg/dL	205.9±41.0	202.8±34.9	0.1078	191.9±41.0	190.0±32.7	0.4335
HDL Cholesterol, mg/dL	61.0±18.1	57.4±15.4	<.0001	49.3±15.6	44.5±11.4	<.0001
Systolic BP, mm Hg	139.5±21.2	131.7±17.9	<.0001	136.3±20.1	130.3±15.9	<.0001
Diastolic BP, mm Hg	78.2±10.6	72.8±9.2	<.0001	81.1±10.9	75.3±9.1	<.0001
Ever Smoker, %	289(30.9)	284(40.5)	0.0001	250(64.4)	326(60.9)	0.2787
Diabetes, %	282(30.1)	92(13.1)	<.0001	109(28.1)	93(17.4)	0.0001
Previous history of MI or stroke	78(8.3)	37(5.3)	0.0164	53(13.7)	55(10.3)	0.1149
Statin Use, %	170(18.2)	165(23.5)	0.008	76(19.6)	197(36.8)	<.0001
Aspirin Use, %	287(30.7)	243(34.6)	0.0906	149(38.4)	267(49.9)	0.0005
Physical activity score	9.6±3.1	12.8±4.9	<.0001	10.2±4.1	14.1±5.6	<.0001
Alcohol (oz)/Month	0.8±3.9	3.1±6.0	<.0001	3.2±7.9	9.1±14.1	<.0001

Table 5: Increased/decreased markers in women and men (irrespective of ethnicity)

	Women		Men		
	Increased	Decreased	Increased	Decreased	No difference
Inflammation	CRP	TNFRI	IL-18	CRP	P-selectin
	SAA	IL-18	TNFRI	SAA	IL-6
	ICAM	TNFRII	TNFRII	ICAM	
	VCAM	MCP-1	MCP-1	VCAM	
	MPO	E-Selectin	E-Selectin	MPO	
	RANGE	Hsp27	Hsp27	RANGE	
	TIMP-2	MMP-2	MMP-2		
		MMP-9	MMP-9		
		TIMP-1	TIMP-1		
			TIMP-2		
Lipoprotein metabolism					
	ApoA-I	Lp-PLA2 mass	ApoA-I	Apoc-III	ApoE
	ApoB	Lp-PLA_2 activity	ApoB	Lp (A)	LDL Size
	ApoC-III		LDL Size	Ox-LDL	
	LDL Size		Lp-PLA_2 mass		
	Lp (A)				
	Ox-LDL				
Adipocyte metabolism					
	Leptin			Leptin	Resistin
	Adiponectin			Adiponectin	

Table 6: Increased/decreased markers in women and men (irrespective of sex)

	AA			WH	
	Increased	Decreased	Increased	Decreased	No difference
Inflammation	CRP	IL-18	IL-18	CRP	IL-6
	ICAM	VCAM	ICAM	MCP-1	E-selectin
	IL-18	TNFRI	TNFRI	HSP27	P-selectin
	MCP-1	TNFRII	TNFRII	MPO	SAA
	P-selectin	RANGE	RANGE	MMP-2	
	HSP-27	MMP-9	MMP-9	TIMP-2	
	MPO	TIMP-1	TIMP-1		
	MMP-2				
	TIMP-2				
Lipoprotein metabolism					
	ApoA-1	ApoC	ApoB	ApoA-1	ApoE
	Lp(A)	Ox-LDL	ApoC	Lp(A)	LDL size
		Lp-PLA_2 mass	Ox-LDL		Ox-LDL
		Lp-PLA_2 activity	Lp-PLA_2 mass		Lp-PLA_2 mass
			Lp-PLA_2 activity		
Adipocyte metabolism					
	Leptin	Adiponectin	Adiponectin	Leptin	Resistin

Table 7: Clinical data evaluation using algorithm shows influencing biomarkers and variables to be considered based on gender and ethnicity

Gender	AA+WH	AA+WH	AA	WH	AA	AA	WH	WH
Ethnicity	Women	Men	Men+ Women	Men+ Women	Women	Men	Women	Men
Type of Biomarkers								
Inflammation	P-selectin TIMP-1/ IL-18	ICAM CRP	VCAM TIMP-1	HSP27 CRP				
LAM	Adiponectin ApoE ApoA-1	Adiponectin	LDL	ApoB				
Basic Variables	Systolic Total cholesterol	Systolic	Smokers Total cholesterol Age PH	Aspirin Smoker Systolic HDL Alcohol	Alcohol PH PAS Diabetes Aspirin	Alcohol PH Diabetes BMI	Alcohol PH PAS Diabetes BMI Statin	Alcohol PH PAS BMI Statin

Yamaguchi *et al.,* 2006), which inturn depends on Src and B-Raf. Other proposed mechanism also showed activation of ubiquitous pathways such as G-proteins by binding Gαi/o proteins (Yuasa *et al.,* 2004), mTOR, PI3-kinase, Jak2-STAT1/3, NFAT (*n*uclear *f*actor of *a*ctivated *T* cells), and NF-kB (*n*uclear *f*actor *k*appa B) signaling (Bhunia *et al.,* 2002; Boca *et al.,* 2006; Shillingford *et al.,* 2006). Many of these pathways involve Ca^{2+} as a second messenger at the primary stage of cyst initialization, and hence these

Table 8: `Analysis of the associated kidney markers co-expressed with CVD markers by pathway analysis using STRING analysis

	CVD Markers	Kidney markers/signalling molecules co-expressed with CVD markers
Inflammation	P-selectin	ITGB2, VWF, ITGB2, STAT6, SELP
	TIMP-1	MMP-9,VEGFA, TGFB1
	IL-18	CASP1, NFKB1, IL1B
	ICAM	ICAM-1, ICAM-2
	CRP	C1S, SERPINE1, TNF, IL-6
	VCAM	ICAM1 NFKB1 SELE, SELPLG
	HSP27	HSPA1A, MAPKAPK3, HSPA8
LAM	ApoE	APOE, CETP , LPL, APOC3, MTTP

pathways strongly reflect cell proliferation involvement. TGF-b signalling is also one of the majors signalling involved in ESRD and is excessively found during the late course of ADPKD pathogenesis. TGF-β cascade actor, SMAD2 phosphorylates and translocates to the nucleus in many human tissues and mice models (Hassane *et al.,* 2010). Cell cycle progression is governed by *c*yclin-*d*ependent *k*inases (Cdks), and its progression is inhibited by p21 through deactivating Cdks. Polycystins have been shown to act in concert with p21 expression and regulate its activity by binding *J*anus *k*inase (JAK) and *s*ignal *t*ransducers and *a*ctivators of *t*ranscription (STAT) pathway. STAT1 and 3 are activated by PC-1 elevating p21 levels and reducing cell growth. Activation of this pathway is very much dependent on PC-2 interaction with JAK2 having an intact PC-1 C-terminus (Bhunia *et al.,* 2002). One of the problems which continue to disrupt fluid sensing mechanism is the planar cell polarity. PC-1 is known to have profound effect on canonical (β-catenin dependent) and non-canonical (β-catenin independent) network of Wnt signaling. PC-1 null cells upregulate Wnt signaling active markers in ADPKD cysts, whichwields a negative effect on the system (Happeì *et al.,* 2011; Lal *et al.,* 2008; Song *et al.,* 2009). The canonical pathway is stabilized through nuclear translocation by β-catenin directly involving upregulation of *PKD1* promoter and its transcription regulation leading to TCF-dependent transcriptional activity (Rodova *et al.,* 2002).

Cell culture experiments have predicted various transcriptional elements regulating *PKD1* promoter. Varying in their roles during gene regulation, different transcription factors have shown different response in regulating *PKD1* gene promoter region. Diverse transcription binding sites have been identified which regulate DNA-protein interaction at gene level, and contributing imperatively to the basic target of gene regulation. *PKD1* promoter region upstream of the transcription start site is a hub of transcription interactions involved in DNA-protein or protein-protein interaction. In the past decade, many of these gene controlling elements have played a crucial role in understanding proper transcription initiation of PKD genes.

Gene modifiers such asPPAR-g, Ets, p53, Sp1, Ap-1, retinoic acid, ZBP-89, E-box b-catenin element (Aguiari *et al.,* 2012; Jeon *et al*; 2007; Lantinga-van Leeuwen *et al.,* 2005; Rodova *et al.,* 2002; van Bodegom 2006, 2010; Yoshihara *et al.*, 2012) have provided an important insight into *PKD1* gene function and its relation to cystogenesis. Despite having their own *cis*-regulatory region with the promoter, these transcription factors also work in concert with various co-activators, which modify and/or enhance their DNA binding capacity through protein-protein interactions. Gene expression often experiences epigenetic modulation during developmental and regulatory processes (Strahl and Allis, 2000) influenced by histoneacetylation and histone deacetylation. These post-transcriptional modifications increase or decrease the accessibility of transcription factors to gene promoter by changing secondary structures of histone proteins bound to DNA strands (Gregory 2001). Growing evidence in polycystin interaction with *h*istone *a*cetyl *t*ransferase (HATs) and *h*istone *d*eacetylase (HDACs) provide a fine tuned mechanism of transcription factors such as Sp1, p53 and β-catenin working in concert with HDAC with a better insight into PKD promoter activity,and its dependence on post transcription modifiers (Eberharter and Becker 2002; Enya *et al.,* 2008; Lin *et al.,* 2008; Verdone 2005).

Sequence Conservation and Evolution of *PKD1*

Sequence conservation and evolution of genes play an important role in studying primate evolution and their relation to other taxa. Mammalian gene evolution and their divergence from lower chordates indicate

close proximity among their nucleotide sequences. This nucleotide divergence has been helpful in studying disease affliction among species and the challenge rose to find conservation among genes and their regulatory sites. Since human chromosome 16 carries the *PKD1* gene at 16p3.3, but it is reiterated in several copies in 16p13.1, comprising six pseudogenes (Martin *et al.,* 2004). Only the 3.5 kb region located at the 3'end of the *PKD1* transcript is unique to humans (Consortium 1994), but in mouse there is only one *PKD1* gene present at chromosome 17 and no further pseudogenes are found (Olsson *et al.,* 1997). It is stated that human chromosome 16 is one of the most enriched chromosomes comprising segmental duplication clustered mainly along the *p* arm indicating creation of new primate gene leading to human genetic variation.

Conservation of the human *PKD1* gene has been studied in various species. Evolutionary studies show that original duplication of *PKD1* may have occurred before gorillas and humans diverged ~8MYA. Genetic evidence from orangutan subspecies from Sumatra and Borneo detected only single *PKD1*-signal using FISH-signal indicating single copy of *PKD1*. Many of the introns have also been studied for their sequence conservation involving intron 30, the largest intron in *PKD1*and the highly conserved last intron 45. Studying intron conservation also reflect the mechanistic approaches involved in splicing mechanisms and gene silencing events in gene regulation and transcription efficiency (Kirsch 2008; Rodova *et al.,* 2002).

Multispecies genome analysis of *PKD1* promoter region shows various regulatory sites of transcription factor to be conserved among mammalian species. Nine elements were found to be conserved within the *PKD1* promoter region including five elements conserved in the pufferfish *Fugu Rubripes*. Binding sites for E2F, E-box, Ets, MZF and ZBP-89 were found to be conserved in the 5'-flanking region of ~600bp of *PKD1* promoter region (Lantinga-van Leeuwen *et al.,* 2005). Hence, species comparison and evolution conservation among genomic studies helps to elucidate causes of evolution, effect on human phenotypes and changes in molecular events during evolution that are important in normal and diseased phenotypes. This not only presents comparative analysis of sequences, but can identify coding and conserved non-coding regions, including regulatory elements important in transcriptional activation of genes.

Clinical Manifestations Involving ADPKD

Signs and Symptoms

Patients with ADPKD are mainly asymptomatic. Some patients experience early clinical symptomatology having severe abdominal pain, enlarged and palpable abdominal mass, kidney stones, urinary tract infections and hematuria which brings them to medical attention (Schrier *et al.,* 2014). Many patients come into attention by getting diagnosed due to positive family history or development of hypertension, which is one of the most complicated symptoms of ADPKD (Chruchill 1984; Ecder and Schrier 2009; Johnson and Gabow 1997) and is thought to be due to activation of renin-angiotensin system. Majority of the patients experience severe abdominal and flank pain which require pain management therapies, but acute abdominal pain and gross hematuria are also observed in patients having ruptured cysts (Grantham 2008). Urinary tract infections are commonly observed during the course of ADPKD. Patients having cysts and renal parenchyma involvement are given antibiotics for upper and lower urinary tracts infections. Once the afflicted patient experiences these symptoms, prolonged fever, weight loss and gastrointestinal symptoms start occurring making therapies even more complicated.

Diagnosis and Screening of ADPKD

An early diagnosis for ADPKD could have beneficial effects of various treatment therapies for the afflicted patients for slowing renal progression, and prevent other extrarenal complications. Total kidney volume and renal cyst volume is strongly correlated with decline of GFRand may be taken as biomarkes to assess kidney health in ADPKD (Fick-Brosnahan *et al.,* 2002; Tangri *et al*., 2017), and is often observed in patients diagnosed with ADPKD. The foremost diagnosis for the patients showing abdominal pain is an abnormal outgrowth of the abdominal area. Once the patient has been tested for various other symptoms developed during ADPKD complications, the patient undergoes renal imaging and ultrasound, which till date has been the most common method of diagnosis, and remains to be the first and foremost approach.

Ultrasound diagnosis has been based on comparing ADPKD type I and type II which compares the frequency of the cysts in the normal unaffected population (Pei 2009). Presence of at least three renal cysts or two in each kidney are sufficient for diagnosis purpose of an individual at risk. The diagnosis criteria for ultrasound for at-risk individual (with positive family history, and between 30-60 years of age) is four cysts distributed bilaterally (Ravine *et al.,* 1994). Identification of cysts by ultrasound *in utero* are rare (1:1100 pregnancies), however, increased echogenecity is the most common ultrasound finding, and has been observed as early as 17thcentury. *M*agnetic *R*esonance *I*maging (MRI) and computed tomography are fast becoming reliable techniques in their sensitivity to detect cysts. Renal volume determined by MRI is an important prognostic marker of an individual patient to determine the progression of the disease (Nascimento *et al.,* 2001; Torres and Harris 2009). Other than MRI, DNA sequence analysis, genetic testing, and DHPLC screening of *PKD1* and *PKD2* have also been carried out in the patients (Pei and Zhao 2008), but these methods including MRI are not cost effective. Various studies although have pointed out that *t*otal *k*idney *v*olume (TKV) is a potential surrogate parameter for disease severity in ADPKD. Recent trials have, therefore, measured TKV by MR to monitor and predict disease progression, which is fast emerging as novel therapeutic strategies for ADPKD (Liebau and Serra 2013). However, reliable scientific markers to observe disease progression are underway in various clinical trials.

Therapeutics Modalities

Understanding the pathophysiology and availability of various animal models has given an edge over conducting clinical trials to test various interventions to identify candidate drugs for ADPKD. Many treatment therapies start out with primary symptoms for the patients such as treatments for hypertension, antibiotics for urinary tract infections, blood pressure control, analgesics for pain *etc*. (Chapman, 2008; Patel *et al.,* 2009). Several potential drug therapies are now available which target signalling pathways leading to dysregulated fluid secretion and cellular proliferation in cystic kidneys. The main pathway operates *via* cAMP accumulation levels in the collecting duct, which is the main site of cyst development and has been targeted by vassopression through V2 receptor antagonists. Aiming at this pathway by OPC-31260 has led to reduced renal levels of cAMP, and significantly inhibited cyst development in ARPKD, ADPKD and nephronphthisis models (Gattone *et al.,* 2003). Tolvaptan, another V2 receptor antagonist showing higher affinity, has also been trailed in mice models showing equal beneficial effects (Wang *et al.,* 2005). Since cAMP has been the main target in reducing disease progression, somatostatin acting on SST2 receptors inhibits cAMP levels in kidney and liver. Octreotide, a metabolically stable analogue of somatostatine, has also seen considerable improvement in reducing cAMP levels in *pck* rat (Masyuk *et al.,* 2003).

Altered intracellular calcium homeostasis is also one of the causes of accumulation of cAMP levels, and proliferative phenotype of the cystic epithelium is another line for treatment by administrating calcium channel blockers such as Triptolide. This strategy induced cellular calcium release through PC-2 by increasing p21 expression, and hence, arrested cystic growth in*PKD1*$^{-/-}$cells. Many CFTR inhibitors have also been shown to slow cyst expansion in MDCK cell culture models, metanephric kidney organ cultures and *PKD1flox/–Ksp-Cre* mice (Magenheimer *et al.,* 2006; Yang *et al.,* 2008).

Activation of the mTOR pathways in PKD occurs through interaction with PC-1. This pathway has been inhibited by Rapamycin, a potential therapeutic agent serving as an immunosuppressive drug. Several rodent models of PKD have shown retardation in cyst expansion by using mTOR inhibitors (Tao *et al.,* 2005; Shillingford *et al.,* 2006). In many ADPKD transplants treatment with sirolimus has shown great improvement in renal volume as compared with calcineurin inhibitors (Qian *et al.,* 2008). AMP-activated protein kinase has also been suggested to have a beneficial effect toward reduction in ADPKD development. This pathway directly inhibits CFTR by phosphorylation and also inhibits mTOR through tuberin phosphorylation. On similar strategies metformin also showed reduction in MDCK cysts growth and kidneys of *PKD1* knockout mice (Takiar *et al.,* 2011).

Cystic tissues usually overexpress *T*umor *N*ecrosis *F*actor-α (TNF-α), TNFR-I, and TNF-α-

converting enzyme by overexpressing another protein FIP2 which interacts with PC-1 and prevents its transport to plasma membrane and primary cilium (Pirson *et al.,* 2008). Increased cyst formation was observed in *PKD2*$^{+/-}$ mice by TNF administration, which was encountered by giving etanercept showing an inhibitory effect. Many inhibitors for cell proliferation, cell cycle and apoptosis hold potential value for treatment of ADPKD. These drugs have targeted Erb-B1 (EGF receptor) and Erb-B2 tyrosine kinase, Src kinase, MEK, and cdk inhibitors (Omori *et al.,* 2006; Wilson *et al.,* 2006). In line with this theory, Roscovitine, a *c*yclin-*d*ependent *k*inase (Cdk) inhibitor and S-CR8 showed cell cycle inhibition, transcriptional regulation and inhibition of apoptosis which showed successful inhibition of cystogenesis in two PKD murine models (Bukanov *et al.,* 2006, 2011), and increased levels of p21 which is down regulated in PKD.

In summary, current knowledge of PKD has immensely helped in supporting the importance of this disorder. However, further understating needs to be established in order to identify molecular markers, sequence analysis to establish therapeutic intervention, which will contribute towards the clinical manifestations that exist in treatment for PKD.

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