

Preface

Polycystic kidney disease (PKD) is one of the most common life threatening genetic disorders caused by single-gene mutations. Its true prevalence is unknown but, based on autopsy studies, it may affect more than 100,000 persons in the United States, and millions more worldwide. It is characterized by the presence of fluid-filled cysts in the nephrons of both kidneys, eventually leading to kidney failure in the majority of affected individuals. PKD is the fourth most common cause of chronic renal insufficiency or end-stage kidney disease (ESKD). Fifty per cent of adult PKD patients will require dialysis or kidney transplantation within their 6th decade.

There are at least two major types of PKD: autosomal-dominant (AD) PKD and autosomal-recessive (AR) PKD. The genes responsible for these two types of PKD, PKD1 and PKD2 for ADPKD, and PKHD1 for ARPKD, have been identified in the past 20 years. In addition to genetic factors, molecular, cellular and epigenetic factors that contribute to the development of PKD have also been unravelled. This book focuses on the basic and clinical aspects of the burgeoning PKD research. It contains the current information on the diagnosis, management and treatment of PKD; the most recent, pertinent and comprehensive information on the mechanisms of cyst formation in PKD; and the latest information on extra-renal manifestations associated with PKD.

Section I provides a comprehensive guide to the diagnosis, management and treatment of PKD under six broad headings: differential diagnosis (chapter 1); management and treatment of childhood PKD (chapter 2); treatment and management of ADPKD (chapter 3); and diagnosis and treatment modalities for symptomatic PKD (chapter 4). Hypertension (high blood pressure) is always one of the earliest symptoms of PKD, developing in most ADPKD patients by the age of 20 or 30. Blood pressure control in PKD is discussed in chapter 5. Chapter 6 summarizes the completed, and ongoing, clinical trials in PKD, allowing basic scientists to readily view how their efforts are currently being translated to the clinic.

Section II of this book covers most of the fundamental molecular and cellular mechanisms underlying PKD and how this knowledge is contributing to the development of potential novel therapeutic agents. This will allow basic scientists and clinicians to conveniently read these side-by-side chapters to review the basis of the diseases they are studying and treating. In chapter 7, and also in chapter 2 of section 1, the authors provide a general summary of the molecular and cellular pathogenesis of childhood PKD and ADPKD, with emphasis on defective intracellular calcium homeostasis and the cellular response to cyclic AMP. These chapters also elegantly tease out the interconnected roles of MAPK/ERK (mitogen-activated protein kinase/extracellular-regulated protein kinase), mTOR (mammalian target of rapamycin), Wnt, JAK (Janus kinase)/STAT, Cdk (cyclin-dependent kinase), and EGFR (epidermal growth factor receptor) pathways in ciliary dysfunction, cyst formation, renal inflammation and fibrosis. Chapter 7 also highlights the application of atomic force microscopy and small angle X-ray scattering (SAXS) techniques

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to address polycystin multimerization properties. This chapter does not assume any previous knowledge, and gives a clear, concise summary of the key theories and the associated historical figures.

Because tolvaptan, a vasopressin V2 receptor (V2R) antagonist, is already clinically approved for the treatment of ADPKD in several countries, a chapter that comprehensively discusses the role of calcium and cyclic AMP in PKD, and the rationale for using tolvaptan to treat PKD has been included (chapter 8).

Apoptosis as a cellular mechanism in PKD has been thought to contribute to cyst expansion. It has been suggested that reduction in apoptosis was associated with a decrease in cyst growth and kidney expansion, although most of the studies were conducted in ARPKD animal models. However, recent evidence has indicated that induction of apoptosis in cyst lining epithelial cells delayed cyst growth in ADPKD animal models, suggesting that under certain conditions enhanced apoptosis may preserve renal structure by eliminating mural cells from cysts that otherwise would proliferate without limit. The roles of apoptosis in ARPKD and ADPKD animal models are extensively reviewed in chapter 9, opening this controversy to all PKD researchers and encouraging further investigation.

High expression of c-Myc has been observed in kidneys of human ADPKD patients, mouse models produced by dysregulation of Pkd1 and Pkd2 gene dosage, and several non-orthologous animal models of PKD. Chapter 10 summarizes the central roles of c-Myc in the pathogenesis of PKD mouse models, and in human ADPKD development and progression.

PKD1 gene product polycystin-1 can be post-translationally modified by cis-autoproteolytic cleavage at the G-protein coupled receptor proteolytic site (GPS) motif, located at the base of the extracellular ectodomain. The role of defective GPS cleavage in the pathogenesis of ADPKD is discussed in chapter 11.

Epigenetics is one of the fastest growing fields of human disease research. Chapters on epigenetics, (chapter 12), and microRNA (chapter 13) highlight how genetic make-up and epigenetics regulate gene expression and protein function. Knowledge of epigenetic factors has yielded an exciting guide to an ongoing clinical trial (chapters 6 and 12) by targeting sirtuin 1 with nicotinamide (vitamin B3) as a potential PKD therapy.

Renal inflammation has recently been linked to cyst progression in PKD. Chapter 14 highlights the roles of renal inflammation, and the involvement of the PKD1 gene in regulating the expression of some of the pro-inflammatory chemo-attractants such as monocyte chemo-attractant protein-1 (MCP-1) and cytokines such as tumor necrosis factor- α (TNF- α).

PKD has also been associated with ciliary dysfunction, and is known as a ciliopathy. Ciliopathies are genetic disorders caused by mutations that affect the structure and

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function of the cilia or basal bodies. This book has two chapters that provide a general review of the structure and mechanosensory function of primary cilium, as well as the contribution of primary ciliary dysfunction to kidney and cardiovascular disease pathogenesis associated with ADPKD (chapters 15 and 16).

Finally, section III focuses on extra-renal complications. The most common extra-renal manifestations or secondary complications associated with PKD are hypertension, acute and chronic pain, extra-renal cysts, intracranial aneurysms, kidney stones, and ESKD. Although several extra-renal manifestations of PKD are discussed in chapters 2 through 5, this section is dedicated for a special set of secondary complications: cardiovascular complications (chapter 16); PKD-associated liver cysts (chapter 17); seminal vesicle cysts in ADPKD (chapter 18); polycystin-mediated craniofacial development (chapter 19); and rapidly progressive glomerulonephritis in ADPKD (chapter 20).

Chapter 17 extensively discusses the pathogenic sequence and genetic profile of liver cyst formation and progression either as a distinct genetic disease in the absence of renal cysts or in ADPKD and ARPKD. The genetic connection between autosomal dominant polycystic liver disease (ADPLD) and ADPKD is also discussed.

Patients with ADPKD are generally known to be fertile. Women with ADPKD usually can complete successful pregnancies. However, as discussed in chapter 18, some men with ADPKD develop conditions that may affect their fertility because of necrospemia (sperm in the semen that are not alive), immotile sperm, seminal vesicle cysts, and ejaculatory duct cysts.

The role of the polycystins in controlling craniofacial development and growth has recently been reported in *Pkd1* and *Pkd2* mutant mice, as discussed in chapter 19. This information may be useful in understanding the interaction between PKD and head growth and development in ADPKD patients. Many cases of rapidly progressive glomerulonephritis (RPGN) have been reported in ADPKD kidneys. As such, the discussion of RPGN in chapter 20 may help clinicians to understand the full spectrum of potential renal manifestations.

This book also provides a broad overview of some of the biggest challenges currently faced by researchers and clinicians in the PKD field. Like all good publications, the biggest problem is that it leaves you wanting more. The intended audience of this book is students, basic scientists and clinicians who are interested in the basic and/or clinical aspects of PKD. The goal of this book is that it would act as an authoritative source for readers who want a comprehensive understanding of the development, progression, management and treatment of PKD.

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