Review

The polycystins: a novel class of membrane-associated proteins involved in renal cystic disease

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Abstract. Polycystin-1, polycystin-2 and polycystin-L are the predicted protein products of the PKD1, PKD2 and PKDL genes, respectively. Mutations in PKD1 and PKD2 are responsible for almost all cases of autosomal dominant polycystic kidney disease (ADPKD). This condition is one of the commonest mendelian disorders of man with a prevalence of 1:800 and is responsible for nearly 10% of cases of end-stage renal failure in adults. The cloning of PKD1 and PKD2 in recent years has provided the initial steps in defining the mechanisms underlying renal cyst formation in this condition, with the aim of defining pharmacological and genetic interventions that may ameliorate the diverse and often serious clinical manifestations of this disease. The PKD genes share regions of sequence similarity, and all predict integral membrane proteins. Whilst the predicted protein domain structure of polycystin-1 suggests it is involved in cell-cell or cell-matrix interactions, the similarity of polycystin-2 and polycystin-L to the pore-forming domains of some cation channels suggests that they all form subunits of a large plasma membrane ion channel. In the few years since the cloning of the PKD genes, a consensus that defines the range of mutations, expression pattern, interactions and functional domains of these genes and their protein products is emerging. This review will therefore attempt to summarise these data and provide an insight into the key areas in which polycystin research is unravelling the mechanisms involved in renal cyst formation.

Key words. Polycystic kidney disease; polycystin; mutations; renal cysts; antibodies; immunolocalisation; signal transduction.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) has been the subject of considerable clinical and scientific interest over many decades. It is a common genetic condition that is inherited as an autosomal dominant trait and affects in excess of 1:1000 of the general population, which represents more than 5 million people worldwide [1]. It is a systemic condition with diverse clinical abnormalities, cystic and noncystic, seen in renal and extrarenal tissues [2]. Disease expression is extremely variable, even within families, which strongly suggests that other genetic or environmental factors may have a role in cyst formation and disease progression [3, 4]. The mechanisms underlying renal cyst formation in ADPKD and other inherited and
acquired conditions are largely unknown. The opportunity to identify the processes involved in cyst formation in this common monogenic condition may therefore provide valuable insights into normal renal cell physiology and the function of other tissues affected in ADPKD, especially the cardiovascular system. The elucidation of the function of the ADPKD genes and the identification of other disease-modifying factors also provides the best opportunity to design interventions that may significantly alter disease progression.

A wealth of data has been collected from a varied multidisciplinary approach to the study of ADPKD which has defined the common anatomical, biochemical and physiological abnormalities seen in renal cysts [5, 6]. Polycystic kidney diseases have been defined as 'genetic or acquired disorders with progressive distension of multiple tubular segments or glomerular capsules, and are manifested by fluid accumulation, growth of non-neoplastic epithelial cells and remodelling of the extracellular matrix resulting ultimately in some degree of renal functional impairment, with the potential for regression after removal of the inductive agents' [7].

Cysts arise from the epithelial cells lining the renal tubule and may occur due to a wide variety of experimental and disease processes, genetic and nongenetic [8–10]. Cysts are seen in the normal ageing population, in the kidneys of individuals with endstage renal failure (ESRF) whose primary diagnosis is a noncystic disorder, and most commonly in the genetic polycystic diseases, ADPKD and autosomal recessive polycystic kidney disease (ARPKD). In ADPKD cysts arise in only a small percentage of nephrons, suggesting that a single PKD mutation is not sufficient by itself to initiate cyst formation. Whilst environmental influences may be involved, it has been suggested that two genetic hits may be required for cyst formation: an inherited germline mutation and an acquired somatic mutation [11]. Focal cyst formation in ADPKD may therefore be analogous to tumour formation in genetic cancer syndromes.

Cyst formation represents one of the limited responses to injury that the kidney may undergo and is likely to be the visible consequence of abnormalities that affect a common final set of cellular functions in renal tubular epithelial cells. As ADPKD is a single gene disorder, studies in this condition will form an important part in dissecting the disease-specific and more general pathways involved in normal renal epithelial cell function and cyst formation. Common abnormalities exist in renal cystic diseases, including abnormal epithelial cell proliferation, abnormal extracellular matrix production and degradation, and altered fluid secretion and cell polarity. It has been suggested that many of these changes may be explained by an alteration in the state of differentiation of the tubular epithelial cells [12]. The protein products of the PKD genes, the polycystins, may therefore be involved in pathways involved in initiating and maintaining tubular cell differentiation. There is an increasing awareness of the systemic nature of ADPKD. Whilst the renal cystic disease predominates in most ADPKD families, many extrarenal features of the disease, both cystic and noncystic, are clinically important. The renal disease in ADPKD comprises progressive renal cyst formation and enlargement with the development of renal insufficiency in the majority of affected individuals [13]. This often progresses to ESRF, with ~ 50% requiring renal replacement therapy (dialysis or transplantation) during their 6th decade. Patients with ADPKD account for approximately 10% of adult cases of ESRF. Other renal complications include massive renal enlargement, cyst haemorrhage and infection, and renal stone formation. Rarely, the cystic manifestations may present in young infants or be detected in utero [14]. This form of ADPKD is often associated with a severe clinical course in infancy, with hypertension and ESRF occurring in childhood. Parents who have had one pregnancy or infant affected with this severe form of ADPKD are at high risk of having a further child with similar features. This risk is not evident in second degree relatives who also have the same PKD mutation, strongly suggesting that coinheritance of a modifying gene from the unaffected parent is responsible for altering disease expression [3].

The most common extrarenal manifestation of ADPKD is hepatic cysts [15]. This is rarely associated with impairment of hepatic function but may present with severe discomfort and abdominal distension in a small number of individuals, usually females. Complications such as cyst haemorrhage and infection may be life-threatening [16]. Cysts may also be found in the pancreas. Of the noncystic manifestations, those in the cardiovascular system predominate. Hypertension is a frequent feature of ADPKD, occurring in up to 75% of patients often well before detectable renal impairment is apparent [17, 18]. Cardiac valvular abnormalities are also commonly reported, with mitral valve prolapse occurring in 25% of patients. Left ventricular hypertrophy, aortic root dilation and congenital heart disease are also seen and contribute to the broadening spectrum of cardiovascular disease seen in ADPKD [19–21]. Intracranial aneurysms (ICAs) occur in 8% of ADPKD patients compared with ~ 1% in the non-ADPKD population and may represent a further focal manifestation of the disease [22]. Rupture leading to subarachnoid haemorrhage occurs at a younger age and has a more severe outcome compared with non-ADPKD ICAs, although the precise natural history of this condition in ADPKD is still unclear. More generalised connective tissue abnormalities have been described in ADPKD,