Persistent progress has been made in the understanding of processes that are responsible for renal cyst formation and progression in hereditary polycystic kidney disease (PKD). Multiple lines of evidence support a role for epithelial cell proliferation, transepithelial fluid secretion, and extracellular matrix remodeling in PKD (1). More recent studies have begun to illuminate intracellular mechanisms that are responsible for abnormal cell proliferation and fluid secretion in PKD.

For many years, investigators have attempted to alter disease progression in animal models of PKD, originally with the intention of testing hypotheses regarding disease pathogenesis. Advances in the understanding of disease mechanisms in PKD have allowed refinement in attempts to alter disease progression, with the idea of testing in human clinical trials interventions that are effective in multiple different animal models. These early steps in developing effective, specific treatments for PKD represent a maturation of the scientific understanding of PKD. At the 2007 Annual Meeting of the American Society of Nephrology, a new feature, “Meeting within a Meeting,” focused on PKD and included a session entitled “New Insights, Treatments, and Management Strategies for ADPKD.” The articles in this Moving Points in Nephrology series summarize the information presented at that session.

CRISP and HALT

Human autosomal dominant PKD (ADPKD) causes complications in multiple organs, including the kidneys. Because the most common, serious complication is ESRD, interest focuses on altering this aspect of ADPKD. With a complication that occurs in only 50% of patients, especially one that progresses slowly, it is difficult to demonstrate efficacy of specific treatments. The ability to monitor disease progression accurately not only will improve the ability to demonstrate efficacy of potential therapies but also may allow targeting treatment to those most at risk for progression. These were some of the major rationales for the National Institutes of Health–sponsored Consortium for Radiologic Imaging Studies of PKD (CRISP). A major finding of CRISP is that magnetic resonance imaging techniques allow accurate estimates of changes in renal and cyst volume over a relatively short time in patients with ADPKD (2). Thus, repetitive monitoring of renal and cyst volume in groups of patients with ADPKD may be used to assess the efficacy of potential therapies. This will be used in the HALT PKD trial in which blockade of the renin-angiotensin-aldosterone system will be studied (2). Although some might consider cyst progression to be a “surrogate marker” for disease progression in ADPKD, it should be emphasized that development and progression of renal cysts are the disease, whereas renal functional deterioration is a complication. A more detailed discussion of CRISP, HALT, and related issues is presented by Chapman (2).

Mechanisms of Cell Proliferation and Fluid Secretion

In humans, ADPKD is caused by mutation in the genes that encode polycystin 1 (PC1) or polycystin 2 (PC2). Progress continues in understanding the normal roles of PC1 and PC2 and how abnormal function of these proteins can result in PKD (3–5). PC1, PC2, and multiple proteins associated with PKD in other animals have been shown to localize to primary cilia, leading to interest in these structures, whose function has been unknown. It has been suggested that cilia act as flow sensors in the tubules, with flow-induced deformation resulting in calcium influx through PC2, which can act as a cation channel. Disrupted function of PC2, PC1 (which can physically interact with PC2 and potentially regulate PC2), or other proteins that are associated with PKD causes abnormal ciliary structure and presumably function, potentially resulting in abnormally low intracellular calcium. Low intracellular calcium can cause a proliferative response to increased intracellular cAMP, which is antiproliferative in normal renal epithelium. Previous studies suggested that cAMP also has an important role in fluid secretion in PKD. Thus, cAMP may have a key role in both cell proliferation and fluid secretion in PKD. Calvet (3) discusses intracellular mechanisms whereby altered PC function can lead to abnormal proliferation and transepithelial fluid secretion in tubular epithelial cells. The abnormal proliferation seems to

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involve abnormal intracellular mitogen-activated protein kinase signaling, whereas abnormal fluid secretion seems to be critically dependent on chloride secretion through CFTR channels.

**cAMP and Vasopressin Receptor Antagonists**

The studies summarized by Calvet support a role for intracellular cAMP in cell proliferation and fluid secretion in cystic epithelia; however, there are numerous mediators that can promote cAMP formation in renal epithelial cells. Studies by Gattone and colleagues (4) in animal models of PKD demonstrated abnormalities of vasopressin and vasopressin receptors, which could result in increased intracellular cAMP generation. This led to in vivo studies of a vasopressin receptor antagonist, OPC-31260, which ameliorated disease in several different animal models of PKD. Human clinical trials in patients with PKD of a related vasopressin receptor antagonist, tolvaptan, which was developed for other clinical purposes, are under way. Torres (4) reviews molecular mechanisms whereby cAMP can promote PKD progression, relevant animal studies of V2 receptor antagonists, and early clinical data regarding use of tolvaptan in patients with PKD.

**Sirolimus, Caspases, Proliferation, and Apoptosis**

The most common, serious complication of ADPKD is ESRD, which occurs in approximately 50% of patients. Emerging evidence supports a role for interstitial inflammation and interstitial fibrosis in renal functional deterioration in PKD, as has been suggested for other types of chronic progressive renal disease. Early animal studies demonstrated amelioration of disease with glucocorticoids (1); however, cyclosporine was ineffective in one rodent model of PKD (unpublished observations). Sirolimus is a newer immunosuppressant that is both antiproliferative and antifibrotic. Edelstein (5) demonstrated amelioration of PKD in the Han:SPRD rat model of ADPKD. Other groups have replicated this finding and expanded it to include other animals models of PKD. Human clinical trials in patients with PKD of a related vasopressin receptor antagonist, tolvaptan, which was developed for other clinical purposes, are under way. Torres (4) reviews molecular mechanisms whereby cAMP can promote PKD progression, relevant animal studies of V2 receptor antagonists, and early clinical data regarding use of tolvaptan in patients with PKD.

**References**


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