Lancing the Cyst with Molecular Methods

Gregory G. Germino

Johns Hopikins Univ., USA

Autosomal dominant polycystic kidney disease is one of the most common genetic disorders of man, affecting all ethnic groups without particular bias. It affects 1/500-1/1000 individuals and is an important cause of end stage renal disease. Mutations of either of two genes, *PKD1* and *PKD2*, have been found to cause ADPKD. The two forms of ADPKD are nearly indistinguishable with overlapping clinical features, differing only in their severity. *PKD1*, the gene mutated in 85% of cases of ADPKD, encodes a large membrane protein that may function as an atypical G-protein coupled receptor. *PKD2*, which is mutated in virtually all other cases of ADPKD, encodes the founding member of the TRPP family of calcium channel proteins. It has been postulated that the two gene products, polycystin-1 (PC1) and polycystin-2 (PC2), form a receptor channel complex in the primary cilium where they function as mechanosensors for luminal flow.

Molecular studies have yielded important insights into the pathophysiology of the disorder. Recent studies suggest that ADPKD1 is likely more severe than ADPKD2 because the *PKD1* gene is more mutable. Mutation studies suggest a possible weak association between the nature of the mutation and disease severity. Other familial factors such as variants at other genetic loci also may be important. However, the most important variable may result from the recessive nature of the disease on a cellular level. Cysts form when the level of functional activity of the PC1/PC2 receptor channel complex falls below a critical threshold.

Presently, it is not known whether somatic mutations are acquired during the lifetime of an individual or during the relatively brief period of fetal development, at a time of rapid cellular proliferation, differentiation and maturation. Gene targeting in mice has been used to create models that recapitulate key features of the human disease. These studies conclusively show that either homozygous germline mutation or acquired inactivation of either gene during renal development results in severely cystic kidneys. However, the published studies do not unambiguously establish a role for these cystoproteins in the maintenance of tubular structure in adult tissue. We therefore tested this hypothesis using a recently described line of mice with a floxed allele of Pkd1 and an inducible Cre-recombinase. We induced inactivation post-natally at a range of timepoints and defined a critical period before which inactivation rapidly results in profound cystic disease in virtually all renal tubules. Inactivation after this time point or in adult mice also results in renal cystic disease but its course differs markedly with respect to its rate of progression. In conclusion, we demonstrate that there is a developmental stage after which loss of PC1 results in relatively mild disease despite continued growth of the animal.

These data suggest that the timing of inactivation of *Pkd1* in the kidney has profound effects on the nature of the cystic disease that results, with important implications for our understanding of the pathophysiology of disease and our use of rodent models to test potential therapies.