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Animals models of autosomal dominant polycystic kidney disease

EDUCATIONAL OBJECTIVES

- Review the current literature on animal models of autosomal dominant polycystic kidney disease
- Evaluate the impact of these models on the knowledge on cystogenesis and therapeutics of ADPKD
- Determine how to improve the currents models and to create more accurate models.

PRESENTATION SUMMARY

Autosomal dominant PKD (ADPKD) is the most common of the inherited renal cystic diseases, a group of disorders characterized by the development of renal cysts and a variety of extrarenal manifestations. Autosomal dominant PKD is genetically heterogeneous with two genes identified, \textit{PKD1} (chromosome 16p13.3) and \textit{PKD2} (4q21). The PKD1 and PKD2 proteins, polycystin-1 (PC1, \approx 460 kDa) and polycystin-2 (PC2, \approx 110 kDa) constitute a subfamily (TRPP) of transient receptor potential (TRP) channels.

The polycystins are essential to maintain the differentiated phenotype of the tubular epithelium. Reduction in one of these proteins below a critical threshold results in a phenotypic switch characterized by inability to maintain planar polarity, increased rates of proliferation and apoptosis, expression of a secretory phenotype, and remodeling of the ECM. The molecular mechanisms responsible for this phenotypic switch are not known.

Animals models linked to PKD1 and PKD2 provide new clues to explore molecular mechanisms. Mouse, zebrafish and cats with reduced expression of polycystins are available. There is no model that is perfectly alike the human disease. Despite this limit, study of transgenic mice provide a new model to explain cyst formation. The cystogenesis in ADPKD is a three hits phenomena with germinal mutation (first hit), somatic mutation (second hit) and cellular proliferation (third hit) is allowing the full expression of the cellular cystic phenotype. This paradigm of cystogenesis permits us to understand the variability observed in humans.

The animals models were used to test new therapeutics. Tolvaptan, inhibitors of mTOR are effective to delay cyst formation in animals models and are currently test in clinical trials.
Despite the fact that animals models do not mimick perfectly the human disease. Their value is incomparable. The futur of this field is in the creation of animals with polycystic kidney disease similar to human autosomal dominant polycystic kidney disease.