

## Renal Cyst Fluid From Human Polycystic Kidney Disease Patients Stimulates Cl<sup>-</sup> Transport: Active Factor and Cl<sup>-</sup> Channels

Bonnie L. Blazer-Yost<sup>1,4</sup>, Brenda Blacklock<sup>2</sup>, Robert L. Bacallao<sup>3,4</sup> and Vincent H. Gattone<sup>4</sup>

<sup>1</sup>Department of Biology  
IUPUI  
Indianapolis, IN

<sup>2</sup>Department of Chemistry and Chemical Biology  
IUPUI  
Indianapolis, IN

<sup>3</sup>Division of Nephrology  
IUSM  
Indianapolis, IN

<sup>4</sup>Department of Anatomy and Cell Biology  
IUSM  
Indianapolis, IN

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the slow growth of fluid-filled cysts predominately in the kidney and in liver bile ducts. The factors involved in modifying the rate of cyst growth through epithelial proliferation or secretion are critical to understanding the progression of the disease. In addition, elucidation of mechanisms that potentiate the normal progression to renal failure will provide the basis for therapeutic intervention. Of note are the observations that the decline in renal function in middle age is precipitous and that renal injury results in an exacerbation of cyst growth. Using electrophysiological and biochemical techniques, we identified LPA (lysophosphatic acid) as a component of cyst fluid that stimulates secretory Cl<sup>-</sup> transport via two anion channels, CFTR and TMEM16a, in the mpkCCD<sub>c14</sub> model of renal principal cells. The LPA effect is manifested through receptors located on the basolateral membrane of polarized renal cells resulting in stimulation of channel activity in the apical membrane. Concentrations of LPA measured in ADPKD cyst fluid and in normal serum are sufficient to maximally stimulate ion transport. Thus, cyst fluid seepage into the interstitial space and/or leakage of vascular LPA are capable of stimulating epithelial cell secretion resulting in cyst enlargement.

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