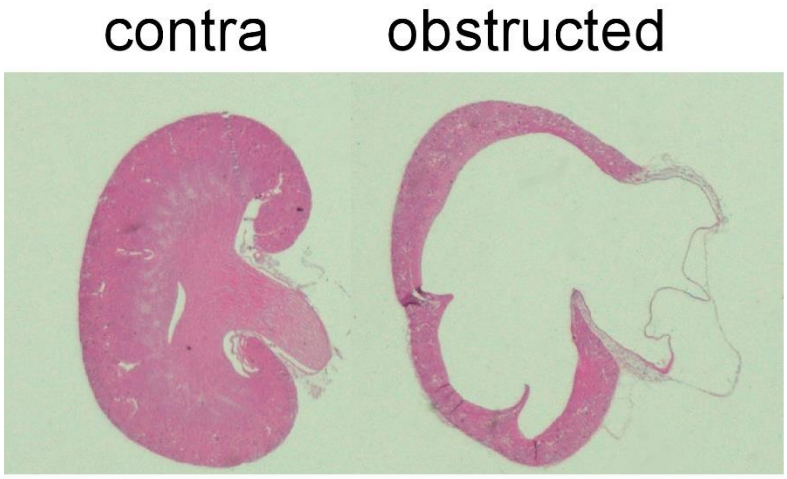
# Project 3: Mechano-nephropathies




In the kidney, important progress has recently been made in the understanding of flow sensing by tubular epithelial cells (*91, 92*). Bending of the primary cilium at the apical side of tubular cells induced by the flow of intraluminal urine activates the ciliary polycystin complex (Polycystin-1; PC1 and Polycystin-2; PC2 which are mutated in autosomal dominant polycystic kidney disease, ADPKD), resulting in a calcium influx through the transient receptor potential (TRP) channel PC2 (for reviews: (*2, 93-95*)). Kidney epithelial cells also respond to changes in intraluminal pressure (*2, 94*). Normal pressure at rest within the renal pelvis and ureter is in the range of 0-10 mm Hg. However, peristaltic pressures generated by rhythmic papillary contractions required for the transport of urine vary between 15 and 45 mm Hg (*2*). When a renal tubule is subjected to intraluminal pressure, both apical and basolateral membranes are stretched (*96*). This physiological transient elevation in pressure is transmitted back to the tubular lumen and leads to repetitive tubular distension and cell stretching. Intraluminal pressure can also be dramatically elevated in kidney disease states (*2*). Indeed, obstructive uropathy is associated with a major increase in intratubular pressure, in excess of 60 mm Hg, leading to tubular circumferential stretch (*97-101*). Stretching, as well as compression of renal epithelial cells also occurs in PKD patients (*2*). Abnormal fluid accumulation in renal cysts causes the cyst wall to stretch (*102-104*). Moreover, growing cysts compress neighboring tubules with upstream accumulation of urine leading to increased intratubular pressure. Stretch of epithelial cells has been proposed to impact on cell proliferation, fibrosis, as well as apoptosis (*28, 97-101, 104*). **Thus, pressure-induced stretch of tubular epithelial cells is relevant to both physiological and diseased kidney conditions (2)**.

We demonstrated that Piezo1 acts as a stretch-activated cationic channel (SAC) in renal tubular epithelial cells and PC2, as well as its pathogenic mutants, inhibit its activity (*105*). Co-immunoprecipitation of PC2 together with Piezo1 in transfected cells is critically dependent on the N terminal domain of PC2. These findings suggest that PC2 may interact via its amino terminal domain, either directly or indirectly, with Piezo1 thereby possibly inhibiting its stretch sensitivity at the plasma membrane. This finding may illustrate the possible role of a dysregulated PC2/Piezo1 functional interaction in some aspects of PKD. Moreover, we demonstrated that Piezo1 is preferentially expressed in the inner medulla of adult mice, where it is critically required for SAC activity in collecting duct cells (*106*). Deletion of Piezo1 in renal epithelial cells impacts on the regulation of urine osmolarity (*106*).

We anticipate that our findings will provide a strong basis to further investigate the pathophysiological role of Piezo1 in kidney disease states associated with an increase in intrarenal pressure, including obstructive uropathies and PKD. We are currently exploring the function of novel PC2 interactors in kidney epithelial cells and their role in renal mechanotransduction (*107*).

## References cited:


**2.** **A. Patel, E. Honore, *Nat Rev Nephrol* 6, 530 (Sep, 2010).**
**28.** **R. Peyronnet *et al.*, *Cell Rep* 1, 241 (Mar 29, 2012).**
**91.** **S. M. Nauli *et al.*, *Nat Genet* 33, 129 (Feb, 2003).**
**92.** **H. A. Praetorius, K. R. Spring, *Curr Opin Nephrol Hypertens* 12, 517 (Sep, 2003).**
**93.** **P. Delmas, *Cell* 118, 145 (Jul 23, 2004).**
**94.** **S. Weinbaum, Y. Duan, L. M. Satlin, T. Wang, A. M. Weinstein, *Am J Physiol Renal Physiol* 299, F1220 (Dec, 2010).**
**95.** **S. M. Nauli, J. Zhou, *Bioessays* 26, 844 (Aug, 2004).**
**96.** **M. E. Jensen, E. Odgaard, M. H. Christensen, H. A. Praetorius, J. Leipziger, *J Am Soc Nephrol* 18, 2062 (Jul, 2007).**
**97.** **M. R. Quinlan, N. G. Docherty, R. W. Watson, J. M. Fitzpatrick, *Am J Physiol Renal Physiol* 295, F1 (Jul, 2008).**
**98.** **R. Rohatgi, D. Flores, *Curr Opin Nephrol Hypertens* 19, 65 (Jan, 2010).**
**99.** **A. T. Wyker, R. C. Ritter, D. Marion, J. Y. Gillenwater, *Invest Urol* 18, 430 (May, 1981).**
**100.** **R. E. Power *et al.*, *J Urol* 171, 457 (Jan, 2004).**
**101.** **F. Cachat *et al.*, *Kidney Int* 63, 564 (Feb, 2003).**
**102.** **H. A. Praetorius, J. Frokiaer, J. Leipziger, *Am J Physiol Renal Physiol* 288, 133 (2009).**
**103.** **D. Derezic, L. Cecuk, *Br J Urol* 54, 93 (Apr, 1982).**
**104.** **G. A. Tanner, P. F. McQuillan, M. R. Maxwell, J. K. Keck, J. A. McAteer, *J Am Soc Nephrol* 6, 1230 (Oct, 1995).**
**105.** **R. Peyronnet *et al.*, *EMBO Rep* 14, 1143 (Dec, 2013).**
**106.** **J. R. Martins *et al.*, *Pflugers Arch*, (Mar 29, 2016).**
**107.** **R. Sharif Naeini *et al.*, *Cell* 139, 587 (2009).**