Coordinate regulation of stretch-activated channels and myogenic tone by polycystins 1 and 2

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Autosomal dominant polycystic kidney disease (ADPKD) is an adult-onset genetic disorder that typically affects the kidneys, liver and cardiovascular system. Clinically, it is characterized by the development of renal cysts that can lead to end-stage renal disease. ADPKD is commonly linked to mutations in either polycystin-1 or polycystin-2 (aka PKD1 and PKD2, or TRPP1 and TRPP2), which are integral membrane proteins associated with cellular ion channel activity. Polycystin-1 is a large surface expressed protein (~4300 amino acids) containing 11 putative transmembrane-spanning segments and an extended extracellular N-terminus that appears to interact with components of the extracellular matrix. Structurally, it resembles a receptor or cell adhesion molecule. Polycystin-2 is a member of the transient receptor potential (TRP) channel family, and is capable of forming calcium-permeable cation channels. Due to its ER retention motif, polycystin-2 is largely localized to intracellular membrane compartments and it remains unclear whether channel activity is expressed at these locations. In complex with polycystin-1, however, polycystin-2 may be trafficked to the plasma membrane where it may form cation-selective channels. Due to its ER retention motif, polycystin-2 is largely localized to intracellular membrane compartments and it remains unclear whether channel activity is expressed at these locations. In complex with polycystin-1, however, polycystin-2 may be trafficked to the plasma membrane where it may form cation-selective channels. Interactions of this complex with other proteins, such as TRPC and TRPV channel subunits, and cytoskeletal elements, have also been reported. Functionally, both polycystins-1 and -2 are thought to contribute to intracellular calcium homeostasis. In the kidney and epi/endothelial layers, there is evidence that polycystin-1 and -2 are involved in mechanosensitivity to fluid flow or shear stress, which may be due in part to their localization at the base of ciliary structures extending from the cell surface. Mechanical bending of these cilia may initiate an elevation of cytosolic free calcium, leading to downstream cellular responses (i.e. endothelial nitric oxide synthesis). Despite our growing knowledge of polycystin biology, key aspects of their cellular behavior remain unclear with respect to mechanosensitivity. In the present study, the authors have investigated the potential role(s) of polycystin-1 and -2 on the pressure-induced activation of stretch-activated cation channels (SACs) and the ability of small resistance arteries to constrict in response to pressure-induced increases in their luminal diameter (i.e. myogenic constriction). In particular, the authors have hypothesized that polycystins may regulate the activity of SACs in vascular smooth muscle, through a mechanism involving the actin cytoskeleton. The physical activation of SACs, leading to membrane depolarization, is a key, early event triggering the calcium-dependent myogenic response in smooth muscle, and may be impaired by abnormal polycystin function.

Experimentally, SAC activity was monitored via cell-attached patch clamp recordings in a variety of cultured cells (i.e. monkey kidney epithelium (COS-7), porcine kidney (LLCPK-1), dorsal root ganglion (F11)), mouse aortic vascular smooth muscle (MOVAS), rat aortic smooth muscle (A7r5) and mouse primary aortic smooth muscle explants) in response to negative pressure pulses applied to the lumen of the recording pipette. Levels of endogenous polycystin-1 and -2 were manipulated by either cDNA-based over-expression or siRNA-based knock down using transient transfection protocols. A
Mechanistically, the authors speculate that polycystin-2 may act in concert with filamin A and other partners to reinforce or stabilize the actin cytoskeleton in the face of increased pressure/membrane stretch, thereby limiting the tension exerted upon evaginations and curved membrane compartments at the cell surface. Because the tension generated within such a microdomain will be proportional to the radius of the structure (Tension = \[\text{Press.} \times \text{radius}\]/2) (Laplace’s law), polycystin-2 may act via the actin cytoskeleton to indirectly regulate SAC activity by limiting the radial expansion of such microdomains in response to stretch, and thus the amount of physical tension exerted upon these mechanosensitive channels. Interaction of polycystin-2 with polycystin-1 may dampen this effect, thereby allowing the development of greater membrane tension, leading to enhanced SAC activity. Given that the suppressive effect of polycystin-2 on SAC activity was observable in multiple cell types, such a model may be broadly applicable, and possibly independent of the actual SAC expressed. The distinct kinetic profiles of the SAC currents observed by the authors in their epithelial, smooth muscle and neuronal cell lines would support such a possibility. In conclusion, this study has presented an interesting and provocative paradigm to explain the regulatory actions of polycystin-1 and -2 on pressure-induced SAC activity and their potential impact on the development of myogenic tone in peripheral resistance arteries.