Nature Reviews Nephrology | Published online 18 Jul 2016; doi:10.1038/nrneph.2016.112

POLYCYSTIC KIDNEY DISEASE

Exiting Ca^{2+} inactivates polycystin-2L1

Polycystin-2L1, a ciliary Ca^{2+}-permeable channel related to polycystin-2, is uniquely inactivated by high intracellular Ca^{2+} concentrations. New research by Paul DeCaen and colleagues shows that exiting Ca^{2+} inactivates polycystin-2L1 through a high-affinity interaction with the Asp523 residue.

Although the cilioplasm and cytoplasm are connected, ciliary levels of Ca^{2+} are higher than cytoplasmic levels; this difference might be related to Ca^{2+}-induced inactivation of polycystin-2L1. "We wanted to understand the structural determinants of this Ca^{2+}-dependent inactivation, a potential feedback inhibition of polycystin-2L1, to shed light on ciliary Ca^{2+} signalling," explains DeCaen.

The researchers measured ionic currents of heterologously expressed human polycystin-2L1 on the plasma membrane using patch clamp electrophysiology, and modulated internal Ca^{2+} levels by photo-uncaging. "This reductionist approach allowed us to mutate polycystin-2L1 and determine the position of residues responsible for the Ca^{2+}-dependent inactivation of the channel," says DeCaen.

> "removal of the C-terminal EF hands … or the coiled-coil domain … of polycystin-2L1 did not alter its inactivation"

Surprisingly, removal of the C-terminal EF hands (Ca^{2+} coordination sites that commonly regulate ion channels) or the coiled-coil domain (which might facilitate subunit oligomerization) of polycystin-2L1 did not alter its inactivation by high intracellular Ca^{2+}. This inactivation was mediated by the high-affinity binding of exiting Ca^{2+} to the selectivity-filter site Asp523. "Our findings suggest that the polycystin-2L1 channel forms a one-way passage by which Ca^{2+} can move across the ciliary membrane — a feature potentially unique to polycystin-2-related channels," notes DeCaen.

Several mutations in *PKD2*, which encodes polycystin-2, are associated with autosomal dominant polycystic kidney disease (ADPKD). "Future work will determine if polycystins set the resting Ca^{2+} levels in primary cilia and if ADPKD-causing mutations alter the Ca^{2+}-dependent inactivation of polycystin channels," concludes DeCaen.

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ORIGINAL ARTICLE DeCaen, P. G. *et al.* Atypical calcium regulation of the PKD2-L1 polycystin ion channel. *eLife* **5**, e13413 (2016)