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POLYCYSTIC KIDNEY DISEASE

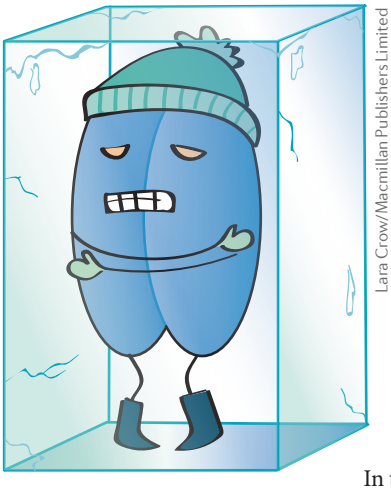
PC2 function: insights from the cold

Altered Ca^{2+} handling by polycystsin-2 (PC2) in the cilium causes autosomal dominant polycystic kidney disease (ADPKD). New structural analyses by Christine Ziegler and colleagues have identified two conformational states of PC2, shedding light on the mechanisms of PC2 inactivation and the role of lipids in PC2 function.

To determine the structure of full-length PC2 in a lipidic environment, Ziegler and co-workers used single particle cryo-electron microscopy, which enables structural studies of flexible membrane proteins. "For PC2, it was the only possible method as the low amount of pure protein was not suitable for crystallization," explains Ziegler.

The researchers uncovered two open conformations of PC2: a single-ion state ($PC2_{SI}$) with one cation bound below the selectivity filter and a multi-ion state ($PC2_{MI}$) with multiple cations bound along the translocation pathway. In particular, binding of Ca^{2+} at a Ca1 site located at the entrance of the selectivity filter in $PC2_{MI}$, might block monovalent cation currents and explain why inactivation of the channel occurs at high Ca^{2+} concentrations.

The two conformational states also differed in the architecture of their TOP domain (a novel highly structured domain), the aperture of the selectivity filter (1.7 Å pore radius in $PC2_{SI}$ and 1.4 Å in $PC2_{MI}$), and levels of *N*-glycosylation (three *N*-glycosylated asparagine residues in $PC2_{SI}$ versus four in $PC2_{MI}$).



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> these conformational changes explain the functional diversity of PC2

"These conformational changes explain the functional diversity of PC2 and also why ADPKD mutations are scattered all over the extracellular and C-terminal domain," says Ziegler. The researchers also showed that lipids mediate interaction between the TOP domain and the P loop (which connects the fifth and the sixth transmembrane helices) in $PC2_{SI}$ but not in $PC2_{MI}$.

In the future, the researchers will study the interaction of PC2 with polycystin-1 and other proteins involved in Ca^{2+} signalling in several organelles such as the primary cilium.

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ORIGINAL ARTICLE Wilkes, M. *et al.* Molecular insights into lipid-assisted Ca2+ regulation of the TRP channel Polycystin-2. *Nat. Struct. Mol. Biol.* http://dx.doi.org/10.1038/nsmb.3357 (2017)
FURTHER READING Grieben, M. *et al.* Structure of the polycystic kidney disease TRP channel Polycystin-2 (PC2). *Nat. Struct. Mol. Biol.* http://dx.doi.org/10.1038/nsmb.3343 (2016)