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POLYCYSTIC KIDNEY DISEASE

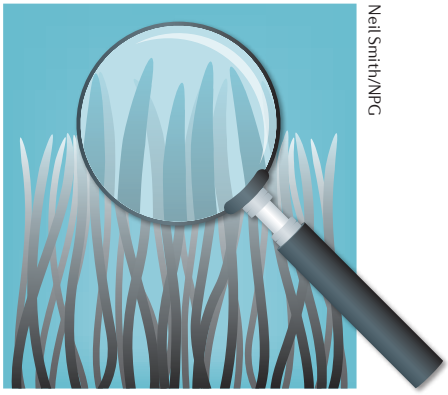
WNTs: ligands of the polycystin complex

> PC1 can function as a co-receptor for WNT proteins coupled to Ca^{2+} signalling

Mutations in *PKD1* and *PKD2* (also called *TRPP2*) cause autosomal dominant polycystic kidney disease, the most common genetic disease of the kidney. The products of *PKD1* and *PKD2*, polycystin-1 (PC1) and TRPP2 are thought to form a receptor–channel complex that regulates Ca^{2+} signalling; however, the extracellular stimuli that activate this complex are unknown. In a new study, Leonidas Tsiokas and colleagues identify secreted WNTs as activating ligands of the PC1/TRPP2 complex through a mechanism that is independent of Frizzled receptors. "Genetic evidence has implicated defects in components of the Wnt pathway in cystogenesis," says Tsiokas. "Our data provide direct evidence that PC1 can function as a co-receptor for WNT proteins coupled to Ca^{2+} signalling, forming the basis for a unifying theory of the mechanism by which defects in Wnt/Ca^{2+} and polycystin signalling pathways lead to cyst formation."

Previous work demonstrating that the cation channel, TRPP2, could be activated via a mechanism involving the small GTPase RhoA, led Tsiokas and colleagues to investigate whether WNT ligands that function through RhoA could activate the PC1/TRPP2 complex. "This idea was also supported by other research showing that partial inactivation of *Wnt9b* in the kidney results in polycystic kidney disease via a mechanism that involves the RhoA protein," explains Tsiokas.

In a series of experiments, the researchers demonstrated that binding of WNTs to the extracellular domain of PC1 activates the PC1/TRPP2 complex to induce whole cell currents and Ca^{2+} influx. Mutated forms of either PC1 or TRPP2 suppressed or eliminated the response to WNTs, indicating that both components of the complex are required for the induction of Ca^{2+} signalling. The use of cell migration assays demonstrated that TRPP2 is required for WNT9b-induced cell migration and studies in *Xenopus* embryos demonstrated that PC1 works within the Wnt pathway to control kidney tubule diameter during pronephric development.



Neil Smith/NPG

"Our study sheds light onto the molecular mechanism by which WNT proteins can induce Ca^{2+} signalling," explains Tsiokas. "Given that WNT proteins can affect multiple organs and tissues at almost every stage of vertebrate development, our study now allows us to pin down the biological role of the WNT/Ca^{2+} limb of the pathway."

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ORIGINAL ARTICLE Kim, S. *et al.* The polycystin complex mediates Wnt/Ca2+ signalling. *Nat. Cell Biol.* http://dx.doi.org/10.1038/ncb3363