Polycystin 1 is an atypical adhesion GPCR that responds to non-canonical WNT signals and inhibits GSK3β

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A recent study demonstrates that PC1 serves as a receptor for Wnt ligands. We find that PC1 responds to Wnt9b by shedding its 350kD N-terminal fragment (NTF), which bears a striking resemblance to the activation mechanism of an adhesion GPCR. For aGPCRs, NTF removal liberates a short peptide sequence near the GPS cleavage site called stachel, which then interacts with an internal binding site and engages a G protein signalling cascade. We find that Wnt9b induces a PC1and Gα13-dependent phosphorylation and inhibition of the GSK3β kinase through the RhoA GTPase-ROCK kinase pathway. Expression of a "constitutively active" aGPCR form of PC1 that lacks its NTF leads to profound suppression of GSK3β activity that is dependent upon RhoA and ROCK. Interestingly, GSK3β is an important negative regulator of the HIPPO/non-canonical Wnt signaling target TAZ(WWTR1), lack of which leads to the development of severe renal cysts. Furthermore, recent data show that pharmacological inhibition of GSK3β is beneficial in mouse models of ADPKD. We find that exogenous expression of an active form of TAZ in PC1 null cells or in PKD1a/b morphant zebrafish suppresses the development of relevant phenotypes. We also demonstrate that pharmacological inhibition of GSK3β leads to accumulation of the TAZ protein and to reduced cystogenesis in a 3D matrigel assay employing PC1 null cells. TAZ abundance and activity have been shown to be upregulated through the non-canonical Wnt signalling pathway. We find that HEK293 cells that express PC1 and PC2 respond to Wnt9b treatment with by significantly increasing TAZ abundance as compared to the wild type HEK293 cells treated in the same manner. Taken together, our data suggest that PC1 is an aGPCR-like receptor for non-canonical Wnt ligands that participates in a novel signalling pathway by linking non-canonical Wnt ligands to the GSK3β-dependent regulation of TAZ, a multifaceted signalling molecule whose absence is sufficient to induce renal cystic disease.