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Interaction of PKD1 with TAZ-Wnt/b-catenin signaling regulates cystogenesis in polycystic kidney disease

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Objectives: Autosomal dominant polycystic kidney disease (ADPKD) is the most common human inherited renal disease, which is caused by mutations of PKD1 or PKD2. Hippo signaling pathway has a critical role in kidney branching morphogenesis and cystogenesis. However, it remains unclear the molecular basis of interaction between PKD1 and Hippo signaling in cystic kidney pathogenesis. Here we identified that role of TAZ as regulator of b-catenin activity underlying the interaction of PKD in development of ADPKD.

Methods: We generated *PKD1$^{fl/fl}$;HoxB7-Cre* mouse by crossing Pkd1-floxed mice with HoxB7-Cre mice and double knockout mice (*PKD1$^{fl/fl}$;TAZ$^{fl/fl}$ HoxB7-Cre)* by crossing *PKD1$^{fl/fl}$;HoxB7-Cre* mice with *TAZ*-floxed mice*. We performed in vitro experiments for the molecular mechanisms of the interaction between PKD1 and TAZ in renal cyst formation using inner medullary collecting duct cell.*

Results: *PKD1$^{fl/fl}$;HoxB7-Cre* mice showed massive renal cystogenesis with highly accumulation of TAZ, b-catenin and c-Myc in the cyst-lining cells. In vitro experiment TAZ interacted with Pkd1 and led to b-catenin inactivation at the basal status, whereas PKD1 deletion promoted TAZ to interact with Axin1, resulting in the increase of active b-catenin by releasing from Wnt destruction complex. In PKD deletion, TAZ translocated into nucleus from cytosol, which induced the expression of c-Myc contributing to kidney cystic formation. In vivo experiments, TAZ deficiency in ADPKD mice (*PKD1$^{fl/fl}$;TAZ$^{fl/fl}$ HoxB7-Cre)* resulted in decrease of active b-catenin as well as c-Myc expression in accordance with reduced renal cystogenesis.

Conclusions: Taken together, our findings suggest that the regulation of TAZ-Wnt/b-catenin by PKD1 is a critical parhogenesis in development of ADPKD and potential therapeutic target.