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A polycystin-2 mutant protein with modified pore properties leads to dilated renal tubules, severe cyst formations and a dysbalance of calcium in collecting ducts

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With an incidence of about 1:1000, autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease. In 15% of the patients, mutations in the PKD2 gene have been identified. PKD2 encodes polycystin-2, an integral membrane protein that acts as a non-selective cation channel. Up to now, however, the underlying mechanism of cyst formation in patients is unknown. An exchange of 11 amino acids in the polycystin-2 channel with that of the related protein polycystin-2L1 results in the selective replacement of the pore region so that the mutant protein is still located in primary cilia and the endoplasmic reticulum. The resulting polycystin-2poreL1 protein leads to dilations of collecting ducts, cyst formation and elongated cilia in homozygous knock-in mice. Furthermore, in calcium imaging assays of these mice increased intracellular calcium levels could be detected after stimulation with vasopressin. Electrophysiological experiments in Xenopus oocytes showed increased calcium currents in oocytes injected with cRNA for polycystin-2poreL1 compared to cRNA for wild-type polycystin-2. In silico homology modeling revealed a wider selectivity filter in our mutant protein compared to the wild-type protein, which supports the higher conductance of calcium in the mutant. From this, it can be concluded that a pore exchange leads to an intracellular dysbalance of calcium levels and subsequent cyst formation in mice, thus emphasizing the importance of the pore region in maintaining tubular geometry in the kidney.

Biography

Katrin Brunner has studied biology for 6 years and subsequently started her research for a Doctoral degree in 2017 at the Institute for Molecular and Cellular Anatomy at the University of Regensburg. Her focus of research lies on structural analyses of Polycystin-1 and functional analyses of Polycystin-2 in association with ADPKD.

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