Polycystins : proteins that regulate the cellular barometer

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The role of polycystins in regulating the cellular barometer, or how ion channels allow cells to perceive membrane stretching. © Eric Honoré / IPMC

What is the role of proteins called polycystins in patients with polycystic kidney disease? A team of researchers from CNRS and INSERM, led by Eric Honoré from the Institut de Pharmacologie Moléculaire et Cellulaire (France) has elucidated the molecular and cellular mechanisms linked to polycystin malfunctions that cause this common hereditary disease. In a study published on October 30, 2009 in the journal *Cell*, Honoré and his colleagues reveal a new biological function for polycystins in regulating pressure sensing.

Adult polycystic kidney disease is a genetic condition that affects about 60,000 people each year in France and for which there is currently no drug therapy. Hypertension is very often the symptom that reveals the presence of this disease, which is characterized by the development of renal, hepatic and pancreatic cysts. Polycystic disease thus affects the kidneys but also other organs, and particularly the cardiovascular system. Indeed, sufferers present with arterial fragility. Although this disease is responsible for 10% of cases of terminal renal failure, the most dangerous complication is linked to the development of intracranial aneurysms that can cause fatal cerebral hemorrhage.

This disease is linked to a malfunction of polycystin proteins 1 and 2 (coded by two genes, PKD1 and PKD2). At the IPMC, CNRS and INSERM scientists led by Eric Honoré have discovered the pivotal role of polycystins in sensing cell pressure. Indeed, they have demonstrated that polycystins 1 and 2 control cell sensitivity to membrane stretching. These proteins, inserted in the cellular plasma membrane, form an ion channel that allows the passage of calcium ions. Because of a genetic mutation that affects the kidneys of polycystic patients, the channels formed by polycystins do not open correctly; calcium fluxes are reduced, triggering cell proliferation and the formation of cysts. It is the ratio between polycystins 1 and 2 that controls this cellular barometer. The inactivation of polycystin 1 in mouse smooth muscle (a vessel wall constituent) caused an inhibition of pressure sensitivity and consequently a drop in vascular tone.

This new biological function for polycystins as a regulator of cellular pressure enables a clearer understanding of the molecular mechanisms underlying the mechanosensitivity of cells. This work has also contributed to elucidating the pathophysiological role of polycystins, and may make it possible to envisage novel therapeutic strategies for the treatment of polycystic kidney disease.

More information: Polycystin-1 and -2 Dosage Regulates Pressure Sensing; Reza Sharif-Naeini, Joost H.A. Folgering, Delphine Bichet, Fabrice Duprat, Inger Lauritzen, Malika Arhatte, Martine Jodar, Alexandra Dedman, Franck C. Chatelain, Uwe Schulte, Kevin Retailleau, Laurent Loufrani, Amanda Patel, Frederick Sachs, Patrick Delmas, Dorien J.M. Peters, and Eric Honore, 2009, *Cell* 139 (doi 10.1016/j.cell.2009.08.045).

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