Roles of aquaporins in kidney diseases

Kenichi Ishibashi
(Dept. of Med. Physiol., Meiji Pharmaceut. Univ.)

Kidneys have eight aquaporins (AQP1/2/3/4/6/7/8/11). Only four aquaporins have significant roles in kidney function as revealed by phenotypes of mice with targeted disruption of each aquaporin. AQP1 is important for general urine concentration. AQP2/3 are important for vasopressin-dependent urine concentration. AQP11 is indispensable for normal function of the proximal tubule as AQP11-null mice die with uremia due to polycystic kidneys at a month old. Roles of other aquaporins are unclear as knockout mice revealed normal phenotypes.

We are interested in AQP11 as it is one of the intracellular aquaporins and has a very low homology with other aquaporins. Such deviated aquaporins are tentatively named super-aquaporins as they are superfamily of conventional aquaporins with less than 20% identities.

Before the formation of renal cysts, AQP11-null proximal tubules were vacuolated at one week old. The vacuoles originate from endoplasmic reticulum (ER). And these cells are eventually cleared by apoptosis at three week old, before the development of cysts. Rapamycin, an immunosuppressant, inhibited cyst growth similar to other polycystic kidney models. AQP11 is indeed a water channel when reconstituted into proteoliposomes.

How can AQP11 at the ER keep intracellular milieu constant in the face of massive water movement at the proximal tubule? Here we face very limited knowledge of intracellular water homeostasis. AQP11 and other members of super-aquaporins including AQP12 are expected to reveal the pathways for intracellular water transport. We hypothesize that the disruption of AQP11 will make proximal tubules vulnerable to osmotic challenge leading cell death with vacuoles.