Autophagy in hypokalemia and AQP2 in autophagy

Jin Kim

*Department of Anatomy and Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul, Korea

Prolonged hypokalemia induces a vasopressin-resistant decrease of urinary concentration and polyuria, which is caused by down-regulation of the expression of aquaporin 2 (AQP2). Abundance of AQP2 is determined by the balance between its production by translation and its removal by degradation or exosomal excretion. Although AQP2 degradation occurs via lysosomes or proteasome, the precise mechanisms underlying this phenomenon remain unknown. Recently, it has been suggested that AVP-mediated phosphorylation can regulate AQP2 abundance. The complexity of AQP2 regulation was revealed by the discovery that AQP2 can be phosphorylated at several sites. Up to now, 7 potential phosphorylation sites on the AQP2 c-terminus have been determined: S226, S229, T244, S256, S261, S264, and S269. Phosphorylation of AQP2 at S256 (AQP2-pS256) and S261 (AQP2-pS261) may inversely regulate the endocytosis and exocytosis of AQP2. AQP2-pS256 is necessary for regulated membrane accumulation of AQP2, which leads to increased water reabsorption and urinary concentration. In contrast, AQP2-pS261 is proposed to stabilize AQP2 ubiquitination and intracellular localization and counterbalances AQP2- pS256. Therefore, the first question is whether autophagy is involved in degradation of phosphorylated AQP2.

Prolonged hypokalemia is a common imbalance potassium levels that can cause defects in urinary concentration ability, i.e., nephrogenic diabetes insipidus in humans and experimental animals, including mice. The collecting duct is the main nephron site where morphological alterations occur in potassium deficiency. Among the various morphological changes that occur in potassium depletion, the most remarkable is the accumulation of cytoplasmic droplets in collecting duct cells. The second question is whether these cytoplasmic droplets induced by hypokalemia are autophagic vacuoles.

Autophagy is a self-digesting process that is essential for the survival of eukaryotic cells, where by unnecessary materials and dysfunctional organelles are sequestered and delivered into lysosomes for

degradation. Interestingly, this process is a catabolic pathway utilized to maintain a balance among the synthesis, degradation, and recycling of cellular components, thereby playing a role in homeostasis. However, until recently, little was known about the connection between autophagy and kidney function. The discovery of autophagy-related genes (ATG) has greatly enhanced our understanding of the mechanisms of the autophagic pathway. Formation of the autophagosome requires two unique ubiquitin-like protein conjugation systems: the Atg5-Atg12 pathway, and the LC3 pathway. Atg7 acts as a catalyst in both conjugation systems and is therefore essential for autophagy. This Atg7/Atg5/LC3-II-dependent pathway is called conventional (canonical) autophagy. In addition, Atg7/Atg5/LC3-II-independent pathway called alternative (noncanonical) autophagy, has recently been described. The third question is; what is the role of conventional or alternative autophagy in degradation of AQP2 induced by prolonged hypokalemia.

In my presentation at the meeting, I will give an overview of the current knowledge about the formation and maturation of autophagosomes, and introduce our group's recent works on the role of the essential autophagy gene Atg7 in degradation of AQP2, especially focused on AQP2-pS256 and AQP2-pS261, induced prolonged hypokalemia.