（書式１８）課程博士

学　位　論　文　要　約

博士論文題目　GATA2 regulates body-water homeostasis through maintaining Aquaporin 2 expression in renal collecting ducts.（転写因子 GATA2 は腎集合管でのアクアポリン２遺伝子発現制御を介して体液バランスを制御する）

東北大学大学院医学系研究科　医科学専攻
生体機能学講座　医化学分野
氏名　于　磊

Body water homeostasis is tightly regulated through the coordinated function of Aquaporin (Aqp) that is expressed in the renal tubular cells. Of the various members of the Aqp family, Aqp1 is expressed in the proximal tubules and is responsible for constitutive reabsorption of water from primary urine. In addition, the final adjustment of urinary osmolality and its volume takes place in the renal collecting duct (CD), which is comprised of principal cells and intercalated cells. Three members of the Aqp family, *i.e*., Aqp2, Aqp3 and Aqp4, are expressed in principal cells of CD and involved in Arginine vasopressin (Avp)-mediated water reabsorption for tight control of body water balance. Aqp2 at the luminal surface of CD reabsorbs water from the tubular lumen to reduce urine volume and maintain systemic blood pressure. Since Aqp2-deficient mice exhibit urinary concentrating defects and polyuria, the importance of Aqp2 for body water balance has been well described**.** The transcription factor GATA2 plays a crucial role in early developmental stages of kidney, while its expression pattern and physiological functions in adult kidney is largely unclear. I examined the tissue distribution GATA2 in kidney of adult mice taking advantages of *Gata2*$^{GFP/+}$ mice, in which GFP fluorescence faithfully recapitulates the endogenous GATA2 expression. Immunohistochemical analysis revealed a robust GFP expression specifically in the renal medulla, where renal collecting ducts are mainly distributed. I found that a series of CD cell-specific markers were abundantly expressed in the flow cytometry-sorted GFP-positive cells, indicating that GATA2 is predominantly expressed in the CD cells. To address physiological function of GATA2 in the CD cells, I generated renal tubular cell-specific *Gata2*-deficient mice (*Gata2*-CKO) by crossing *Gata2* floxed mice with renal tubular cell-specific and doxycycline-inducible *Pax8*-Cre mice. I found that the *Gata2*-CKO mice exhibited high 24-hr urine volume and low urine osmolality, two important signs of diabetes insipidus. Consistently, the *Gata2*-CKO mice showed a significantly decreased level of Aqp2. To address the molecular mechanism underlying the GATA2-*Aqp2* regulatory axis, I introduced biotin-tagged GATA2 into a mouse CD-derived cell line and performed chromatin pull-down assays. Our result revealed direct GATA2-binding to conserved GATA motifs in the *Aqp2* promoter region. A luciferase reporter assay by using an *Aqp2* promoter-reporter showed that GATA2 trans-activates

Aqp2 promotor activity through the GATA motifs. These results thus demonstrate that GATA2 contributes to the maintenance of the body-water homeostasis by directly transactivating the *Aqp2* gene expression in CD cells of adult mouse kidney.