学位論文抄録

Nephric duct lineage-specific role of non-muscle myosin II in mouse kidney development
（マウス腎臓発生における非筋肉型ミオシンIIの腎管系譜特異的な役割の検討）

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Abstract of the Thesis

Background and purpose: During kidney development, formation of the functional urinary exit tract depends on correct sprouting of the ureteric bud (UB) from the nephric duct (ND). In these morphogenetic processes, the roles of Ret signaling are well established. However, the regulatory roles of intracellular cytoskeletal proteins remain unclear. In this project, I have studied the role of two non-muscle myosin heavy chains, IIA and IIB, by deleting both *Myh9* and *Myh10* genes encoding these proteins from ND/UB lineage cells in mice.

Methods: *Myh9/Myh10* were deleted from ND/UB lineages by crossing $Myh9^{flox/flox}Myh10^{flox/flox}$ mice with *Hoxb7Cre* mice. They were analyzed at birth and various embryonic days (E), including E10.5, E11.5, and E14.5, by histology (section immunofluorescence staining and *in situ* hybridization as well as whole mount immunostaining).

Results: Deletion of *Myh9/Myh10* from ND/UB lineages in mice resulted in hydronephrosis/hydroureter at birth due to misconnection/physical blockade between the ureter and bladder. This hydronephrosis/hydroureter was likely to happen because of basally protruding epithelial cells and thus formation of ectopic UB at mid-gestation. Moreover, apical constriction and E-cadherin-mediated intercellular adhesions were reduced in the epithelia, which likely caused the apical extrusion of cells into the lumen followed by massive luminal apoptosis. Genetic suppression of tyrosine kinase receptor (*Ret*) did not rescue these phenotypes, which indicates involvement of a Ret-independent pathway. However, mutant cells exhibited hyperactivation of extracellular signal-regulated kinase (ERK). In vitro culture of mutant kidney rudiments in the presence of an ERK inhibitor partially ameliorated the phenotypes, thus indicating the involvement of Ret-independent mechanisms.

Conclusion: In developing kidneys, non-muscle myosin II is essential for maintenance of the apicobasal integrity of renal epithelia.