Regulation of mineralocorticoid receptor signals in the kidney

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Hypertension affects one billion people world-wide and contributes to a global burden of cardiovascular disorder. Clinical and basic studies have identified renal salt handling as a critical determinant of human blood pressure. Steroid hormone aldosterone and its receptor, mineralocorticoid receptor (MR), play a central role in the kidney fluid system by orchestrating diverse functions of the different cells in the distal nephron, i.e., distal convoluted tubule cells, principal cells, and intercalated cells of the collecting duct. Importantly, MR is the promising drug target for the treatment of hypertension, heart failure, and chronic kidney disease.

In an effort to characterize pathways regulating electrolyte handling in the distal nephron, we have unexpectedly discovered a novel mechanism that regulates MR function in a cell-selective manner. Using mass spectrometry, we have mapped 16 phosphorylation sites in human MR, and have identified a phosphorylation site in the ligand-binding domain that prevents ligand binding and activation (Shibata et al. Cell Met 2013). In the kidney, phosphorylation at this site is found exclusively in intercalated cells of the collecting duct, regulating electroneutral salt reabsorption mechanisms involving these cells. Moreover, this site is regulated in opposite directions by volume depletion and hyperkalemia, controlling the balance between salt reabsorption and potassium secretion in high aldosterone states. We are defining the detailed signaling pathways and their pathophysiological roles in hypertension and kidney disease.

Recent studies have identified that Kelch-like 3 (KLHL3) and cullin-3 (CUL3), partners in cullin-based ubiquitin ligase complex, are novel players in blood pressure homeostasis, mainly through the regulation of electrolyte flux pathways in the distal nephron. In this context, we have shown that this ubiquitin ligase targets WNK kinases for degradation (Shibata et al. PNAS 2013), and that angiotensin II signaling negatively regulates its activity via protein kinase C-mediated phosphorylation at the substrate targeting domain of KLHL3 (Shibata et al. PNAS 2014). These pathways are also involved in modulating the function of MR downstream effectors, maximizing renal salt reabsorption while inhibiting K^+ secretion in volume depleted condition.