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Physiology and pathophysiology of claudins in the kidney

Gheun-Ho Kim
Hanyang University Medical Center, Korea

Solute or water is transported via the transcellular or paracellular pathway across the renal tubular epithelial cells, and the junctional complexes are located in the paracellular route, comprising tight junction (TJ), adherence junction, and desmosome. Three components of transmembrane bridging proteins in the TJ are claudin, occludin, and junctional adhesion molecule (JAM), and the claudins are members of a large family of TJ proteins including at least 26 isoforms with two extracellular loops determining the paracellular ion selectivity and interactions.

Different claudins are located to exert their physiologic actions along the nephron segments from the glomerulus. Claudin-1 is normally located in the Bowman's capsule, but albuminuria can occur when the expression of claudin-1 increase to reach the podocytes. On the other hand, claudin-5 and claudin-6 are localized in the glomerular podocytes, and their pathophysiological significance was unknown.

In the proximal tubule (PT), claudin-2 forms paracellular channels selective for small cations like Na^+ K^+, and Ca^{++} and is also permeable to water so that 20–25% of proximal water absorption may occur paracellularly. Cations and water share the same pore, where the amino acid residues in the first extracellular loop of claudin-2 line the narrowest portion. Claudin-10 has two splice variants, -10a and -10b. They are respectively located in the PT and thick ascending limb (TAL); Claudin-10a acts as an anion-selective channel in the PT, and claudin-10b functions as a cation-selective pore in the TAL. Claudin-16 and claudin-19 mediate paracellular transport of cations such as Na^+, Ca^{++} & Mg^{++} in the TAL, where the expression of claudin-3/16/19 and claudin-10b are mutually exclusive.

The claudin-2 gene mutation or polymorphisms are associated with hypercalciuria and increased risk of kidney stones. The claudin-16 or claudin-19 mutation causes familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC). Claudin-19 disorder accompanies severe ocular defects and was classified as type 2 FHHNC. The phenotype of claudin-14 mutation is deafness without renal manifestations. Claudin-10b mutation produces HELIX syndrome, encompassing hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia, suggestive of abnormalities in renal ion

transport, ectodermal gland homeostasis, and epidermal integrity.

Hypercalciuria and magnesuria in metabolic acidosis are related to downregulation of PT and TAL claudins. The protein expression of claudin-2, claudin-16 and claudin-19 decrease in rats with chronic metabolic acidosis. Upregulation of claudin-14 and calcium sensing receptor negatively acts on the claudin-16/19 complex.

In the collecting duct, claudin-3 acts as a general barrier for ion. If this barrier is disturbed, urine pH may increase, resulting in renal tubular acidosis. Claudin-7 forms a non-selective paracellular channel facilitating Cl^- and Na^+ reabsorption in the collecting ducts. Claudin-4 and -8 serve as anion channels, mediating the paracellular chloride transport or "chloride shunt", which is coupled with transcellular Na^+ reabsorption via the ENaC. Accordingly, claudin-4 or -8 upregulation may contribute to pseudohypoaldosteronism II and/or salt-sensitive hypertension.

In conclusion, claudins have regulatory roles in transporting ions and solutes through the paracellular pathways along the nephron. Their interaction with transcellular transporters and pathophysiological significances in human diseases remain to be elucidated.