IN MULTICELLULAR ORGANISMS, epithelial sheets function as a barrier between two compartments via their ability to form tight junctions (TJs), which regulate the diffusion of fluid, electrolytes, and small molecules through the paracellular pathway. Members of the relatively recently described Claudin (Cldn) family of integral membrane proteins, with at least 23 distinct members in mammals, are the major structural and functional components of TJ strands and are considered to be the best candidates for forming paracellular channels (3, 4, 6, 15). Similarities and differences between Cldn family members and their diverse expression patterns are thought to provide the molecular basis for the heterogeneous features of the paracellular permeability barriers, including differences in the degree of “tightness” and ion selectivity, manifested in different tissues and organs.

The mammalian nephron constitutes a particularly interesting model of barrier diversity, with significantly different paracellular transport along the various tubular segments (4). Both barrier function and ion selectivity have been developmentally and functionally correlated to the presence of at least 12 distinct Cldns, expressed in temporally and spatially distinct patterns during development, with a spatial pattern thought to reflect ultimate TJ functionalities in adult kidney (4, 8). Among several of these that have been studied in considerable detail with results supporting a role in ion selective functions (e.g., Cldn2, -16, and -19) (7, 16), Cldn7, in particular, has been found to be highly expressed in the distal convoluted tubules and collecting ducts of the mature kidney (9, 11), suggesting that it may play an important role in renal NaCl and K+ handling. Support for this premise came initially from studies in vitro in which Alexandre and colleagues (2) overexpressed Cldn7 in the epithelial cell line LLC-PK1 and found increased transepithelial electrical resistance and decreased dilution potentials because of decreased paracellular Cl− conductance and increased paracellular Na+ conductance compared with control cells. In an extension of these studies, Alexandre et al. (1) showed the importance of specific negatively charged amino acids in the Cldn7 extracellular loop in paracellular permeability and charge selectivity by testing Cldn7 mutants with amino acid substitutions in the extracellular domain also in kidney epithelial cells.

Now, in what must be considered the “icing on the cake” experiment, Tatum and colleagues (13) have ablated Cldn7 in mice and found that, although Cldn7+/− mice are viable at birth, they die within 12 days after birth from severe salt wasting and chronic dehydration, with significantly increased urinary Na+, Cl−, and K+ compared with Cldn7−/− mice. Further analysis indicated that Cldn7−/− mice display dramatically increased aldosterone synthase mRNA and increased epithelial Na+ channel-α, Na+/Cl− cotransporter, and aquaporin2 mRNA levels, presumably a compensatory response to the loss of electrolytes and fluid. These mice will prove invaluable for dissecting the complex signaling pathways linking the extracellular domain activities vs. cytoplasmic tail activities of Cldn7 in electrolyte homeostasis in the kidney.

More generally, the striking, and specific, phenotype of Cldn7−/− mice helps to solidify the hypothesis that specific Cldns play unique and apparently tissue-specific functional roles for which other Cldn family members, even quite closely related Cldns, cannot compensate. This is in spite of growing evidence that modulation of expression of at least certain Cldn family members results in often quite dramatic changes in other Cldn family members, the latter contributing to at least some of the phenotypic consequences manifested in cells, tissues, and organs with dysregulated Cldn expression (5, 10, 12, 14). Many Cldn family members remain to be explored with knockout, knockin of mutated forms, and overexpression approaches before we will have a complete picture of the manyfold functional and regulatory activities of the multiple domains and motifs of this diverse family. Nevertheless, the work by Tatum and colleagues (13) moves us forward enormously in understanding biochemically and molecularly how structurally morphologically well-recognized TJs achieve their exquisite diversity of functions in the whole organism.

REFERENCES


