FUNCTIONAL CROSS TALK BETWEEN ENaC AND PENDRIN

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Epithelial Na⁺ channels (ENaC) are expressed in the aldosterone-sensitive distal nephron, where they serve as the final site of renal Na⁺ reabsorption and participate in the regulation of extracellular fluid volume and blood pressure. ENaC gain-of-function mutations are associated with hypertension, whereas loss-of-function mutations are associated with hyponatremia. Appreciation of the features that regulate ENaC expression and activity contributes to our understanding of the role of the kidney in the regulation of blood pressure.

ENaC structure, assembly, and maturation. ENaC is assembled into a presumed trimeric structure (αβγ) from three highly homologous subunits within the endoplasmic reticulum (ER), although higher ordered stoichiometries have also been proposed (3, 12, 21). The assembly appears to be inefficient given that only a limited fraction of newly synthesized subunits are eventually found in channels that reach the cell surface (16, 26). Each subunit exhibits intracellular NH₂ and COOH termini, two transmembrane domains, and a large extracellular loop (ECL) with numerous sites for N-linked glycosylation (2, 3). Immature channels that exit the ER are subsequently processed by remodeling of the N-linked glycans and proteolytic cleavage of the ECLs (5, 6).

Data published in recent years clearly indicate that ENaC is activated by proteolytic release of small inhibitory peptides from the α- and γ-subunits (1, 4). Noncleaved ENaCs exhibit a low open probability (PO). The trans-Golgi network (TGN)-localized protease furin cleaves γ at one site but α at two sites, releasing a 26-mer inhibitory peptide from α and producing a channel with moderate PO (4). Subsequent cleavage of ENaC by prostasin releases an additional 43-mer peptide from the γ-subunit, producing a channel with a very high PO (1). Interestingly, ENaCs with mutated cleavage sites and lacking the inhibitory sequences are active, indicating that release of the inhibitory peptides rather than cleavage per se activates the channel (1, 4). This conclusion is supported by findings that endogenous ENaCs in cortical collecting duct cells and human airway cells, as well as mouse ENaC expressed in Xenopus oocytes, are inhibited by synthetic versions of the α 26-mer and γ 43-mer peptides (1, 4). Noncleaved channels are also present on the cell surface and can be activated by exogenous proteases, providing a putative reserve of ENaC that can be rapidly activated (7).

In whole-animal studies of renal ENaC regulation by hormones, drugs, toxic compounds, or pathological conditions, a shift from an 85-kDa form of γ to a 70-kDa form of γ has consistently been associated with states of increased ENaC activity (8, 9, 15, 19, 22). The 70-kDa form likely results from proteolytic processing of the full-length 85-kDa form by one or multiple cleavage events.

Pendrin regulation of ENaC expression and activity. Kim et al. (10) now report that Scl26a4 null mice lacking the Cl⁻/HCO₃⁻ exchanger pendrin exhibited a blunted increase in blood pressure and renal ENaC activity and subunit levels, in response to either dietary sodium restriction or aldosterone administration. No changes were noted in 1) other renal epithelial Na⁺ transporters, 2) levels of ENaC subunits in colon and thyroid, and 3) circulating levels of renal, adrenal, and thyroid hormones, as well as vasopressin action (10). Altogether, their findings are consistent with a renal-specific pendrin-mediated regulation of ENaC expression and activity. Pendrin and ENaC are both localized in the aldosterone-sensitive segment of the renal nephron. However, they reside in different cell types that do not communicate through gap junctions (10, 13). As increases in levels of expression of α-, β-, and γ-ENaC were blunted in response to aldosterone in Scl26a4 null mice compared with normal mice (10), the regulation of ENaC subunit transcription may be compromised by local alterations in ion transport in the absence of pendrin. The mechanism for this type of regulation is unknown.

The authors also noted that the “cleaved and activated” 70-kDa form of γ-ENaC was preferentially reduced in Scl26a4 null mice compared with normal mice treated with aldosterone (10). This observation suggests that pendrin also regulates ENaC by reducing the fraction of the channel activated by proteases. A reduced fraction of “cleaved and activated” ENaC could result from 1) an increase in the degradation of subunits and/or a decrease in the assembly of αβγ-ENaC within the ER, 2) a decrease in the fraction of ENaC processed while traversing the Golgi complex and TGN (compared with the pool that seemingly bypasses this step), 3) a decrease in the levels of channel-activating-proteases (CAPs, such as prostasin) or a decrease in the residence time for the channel on the cell surface, or 4) changes in the ratio of protease and protease inhibitor at the cell surface (11, 14, 17, 20, 23, 24). As Kim et al. (10) observed normal redistribution of ENaC from cytoplasmic vesicles to the apical plasma membrane of principal cells in the null mice after aldosterone infusion, the mostly likely site of pendrin-dependent regulation of ENaC maturation may very well be in a postbiosynthetic compartment and involve proteases or protease inhibitors present in the tubule lumen. Loss-of-function mutations in the human Scl26a4 gene are associated with deafness, and new data indicate that Scl26a4 knockout in mice causes both deafness and acidification of the vestibular lumen (18, 25). Thus the question now arises: Do pendrin-dependent alterations in renal tubule luminal pH affect the activity and/or levels of expression of proteases that cleave and activate ENaC?

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Editorial Focus
NOTE ADDED IN PROOF

Jasti et al. Nature 449: 316–323, 2007) recently published the crystal structure of ASIC1 showing that it is a homotrimer. As ENaC and ASIC are both members of the degenerin family of channels with high amino acid homology, ENaC may also be an α1β1γ1 heterotrimer.

REFERENCES


