COMMD1 and ion transport proteins: what is the COMMection? Focus on “COMMD1 interacts with the COOH terminus of NKCC1 in Calu-3 airway epithelial cells to modulate NKCC1 ubiquitination”

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Over the past decade, COMMD1 (copper metabolism MURR1 domain containing protein 1) has been regularly identified to interact with ion transport proteins. What do we know about COMMD1, and is there a common ion transport regulatory role for COMMD1? COMMD1 is evolutionarily conserved, and codes for a 21-kDa protein composed of two domains: a COOH-terminal COMM domain found in nine other COMMD proteins, and a nonconserved NH2-terminal domain (6). COMMD1 has a wide tissue expression pattern, is located in the cytosol and nucleus, and colocalizes with early and late endosomal markers (2–4), maybe through interaction with phosphatidylinositol 4,5-bisphosphate (2). COMMD1 has no known enzymatic function and is hypothesized to be an adaptor or scaffold protein.

Initially, COMMD1 was reported to regulate copper transport after dogs suffering from liver copper toxicosis were found to have COMMD1 loss of function mutations (11). Although COMMD1 genetic variations are not linked to human copper overload disorders, COMMD1 does interact with the ATP7A and ATP7B copper transporters, which contain mutations in human copper deficiency or overload diseases (8). COMMD1 was identified through a yeast two-hybrid screen to interact with the δ-subunit of the epithelial sodium channel (ENaC) and subsequently three other ENaC subunits (α, β, γ) (1, 5). Although the in vivo function of δENaC is unknown, the αβγENaC channel forms an aldosterone-induced, amiloride-sensitive apically located Na+/Cl− absorption pathway in distal epithelia. Specific mutations in ENaC genes cause hypo- or hypertension through alteration of distal nephron Na+/Cl− absorption. The cystic fibrosis transmembrane conductance regulator (CFTR) is also located in epithelia and forms an apically located Cl− and HCO3− secretion pathway, which is attenuated when CFTR contains mutations causing cystic fibrosis leading to multiple symptoms including respiratory dysfunction. In the lung, Na+/Cl− absorption and Cl− secretion pathways may be coregulated; therefore it was interesting that COMMD1 was also found to interact with CFTR via a two-hybrid screen (4). Figure 1 depicts a hypothetical cell showing the locations of COMMD1-regulated ion transport proteins.

In this issue of American Journal of Physiology-Cell Physiology, Smith et al. (9) report the Na-K-2Cl cotransporter 1 (NKCC1) as another COMMD1-regulated ion transporter. NKCC1 has a general role in cell volume regulation and specific roles in epithelial Cl− secretion and vestibular function. Smith et al. report that a yeast two-hybrid screen with the cytoplasmic COOH-terminal region of NKCC1 bound COMMD1, and that the NH2-terminal domain of COMMD1 interacts with NKCC1. A COMMD1 1–47 amino acid peptide was sufficient to both stabilize NKCC1 at the cell surface of Calu-3 airway epithelial cells and increase baseline bumetanide-sensitive 86Rb uptake, indicative of NKCC1 activity. In contrast, transient knockdown of COMMD1 in Calu-3 cells did not alter baseline or sucrose-induced activation of NKCC1 activity, but resulted in reduced basolateral NKCC1 and prevented a sucrose-induced transient increase in basolateral NKCC1 population, suggesting a complex regulation of NKCC1 by COMMD1.

COMMD1 has a wider role in cellular physiology as it interacts with NF-κB and HIF-1α transcription factors, HSP70, and proteins in the DNA damage response network (6, 10). What is the link between COMMD1 and this diverse range of proteins? At present, COMMD1’s ability to alter protein stability is the best candidate for a universal COMMD1 function. Extensive study in the NF-κB pathway showed that COMMD1 promotes ubiquitination of NF-κB subunits, thus targeting NF-κB for degradation and decreasing NF-κB-mediated tran-
 movement of ATP7A/B from the Golgi to the cell periphery. At the cell surface, COMMD1 may promote ENaC endocytosis through increasing ENaC ubiquitination (3), or have the opposite effect on CFTR (4). For NKCC1 there appears to be a trend for COMMD1 to stabilize NKCC1 at the basolateral membrane and to also play a role in NKCC1 recycling (9).

What roles are played by COMMD2–10? Their in vivo functions are mostly unknown; however, COMMD proteins dimerize via their conserved COMM domains therefore homo- and heterodimers likely occur in vivo (6). Functional redundancy may disguise experimental observations focused on COMMD1, although COMMD1−/− mice are embryonic lethal, suggesting that unique functions exist for COMMD proteins (10).

To advance our understanding of COMMD1 effects on ion transporters, future studies should include 1) identifying other ion channels and transporters that interact with COMMD1 with the aim of identifying conserved COMMD1 binding motifs, 2) determining the mechanisms by which COMMD1 increases ubiquitination of some proteins and decreases that of others, 3) identifying the COMMD1-regulated ubiquitin ligases that target ion transport substrates, and finally, 4) ascertaining the type(s) of ubiquitin chains linked to ion transport proteins. In conclusion, COMMD1 has an intriguing but underexplored connection to ion transport proteins that are crucial for homeostasis and implicated in a variety of pathophysiological conditions.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS
F.J.M. drafted the manuscript; edited and revised the manuscript; approved the final version of the manuscript.

REFERENCES