ERp29, a chaperone protein ushering in new insights on ion transport regulation. Focus on “ERp29 regulates epithelial sodium channel functional expression by promoting channel cleavage”

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MOLECULAR CHAPERONES of the endoplasmic reticulum (ER) facilitate folding, oligomerization, maturation, and posttranslational modification of nascent polypeptide chains. ER protein 29 (ERp29) is a chaperone protein with high sequence homology to the protein disulfide isomerase family of enzymes, which catalyze posttranslational modification of disulfide exchange. However, ERp29 lacks the thioredoxin motif and is, therefore, regarded as a redox-insensitive member of this family of compounds (8). Although ERp29 is ubiquitously expressed, it is abundantly enriched in the rough ER of actively secreting epithelial cells and complex neurons, where it plays a major role in protein folding (7, 9).

Epithelial Na\(^+\) channel (ENaC) subunits (α, β, and γ) are synthesized in the ER before further folding, glycosylation, assembly, and transport to the plasma membrane as an oligomer (reviewed in Ref. 2). Regulation of synthesis and maturation of ENaC plays a critically important role in maintaining total body fluid homeostasis (i.e., blood pressure) and appropriate lung fluid volumes for effective gas exchange in the terminal airways. Therefore, much attention is focused on ENaC regulatory pathways and potential disruptions of normal signaling pathways that can cause disease. In this issue of American Journal of Physiology-Cell Physiology, Grumbach et al. (6) report an important role for ERp29 in the regulation of functional ENaC expression in Madin-Darby canine kidney (MDCK) cells and in the immortalized cystic fibrosis (CF) bronchial epithelial parent cell line CFBE410 (6). A novel outcome of this report is the finding that ERp29’s single cysteine residue C157 plays an important role in the regulation of ENaC cleavage and the resultant increase in ENaC open probability. Moreover, the authors bridge a large gap in our scientific knowledge concerning ENaC biogenesis by discovering that ERp29 interacts with β-ENaC to promote its association with the Sec24D cargo recognition component of COP II, the coat protein complex responsible for vesicle budding from the ER. Figure 1 highlights these major findings and places ERp29 within the context of basic secretory pathways in the cell.
The Rubenstein laboratory also recently reported a critically important role for ERp29 in the restoration of ΔF508 CF transmembrane conductance regulator (CFTR) function following sodium 4-phenylbutyrate (4PBA) treatment in CF and non-CF epithelial cells (10). Although the precise mechanism is uncertain, the important implication of this finding is that targeting chaperone proteins, such as ERp29, may provide novel mechanistic-based therapies for severe protein trafficking mutations, such as ΔF508 CF.

Together, these studies from the Rubenstein laboratory provide intriguing first steps toward understanding the role of ER chaperone proteins in ion transport regulation in health and disease. However, several questions remain. 1) Although ERp29 lacks the CXXC thioredoxin motif found in other protein disulfide isomerase family members (5), it is not clear that this chaperone protein does not have the capacity to respond to oxidative signaling. A growing body of literature indicates that the effects of reactive oxygen and nitrogen species can be modulated through covalent modification of specific cysteine residues (reviewed in Ref. 3). Moreover, structural alignments performed for proteins from the thioredoxin family (including ERp29) show no apparent differences in the three-dimensional structures between redox-active and -inactive proteins (8). The important implication of this observation is that ERp29 cannot be ruled out as a redox-inactive chaperone protein on the basis of its dissimilarity in sequence alignment. As such, it would be interesting to examine the functional properties of ERp29 and its role as an ion channel chaperone from the ER to the Golgi under prooxidizing conditions. Previous reports have shown that reactive oxygen species upregulate ENaC number and open probability (4), an observation consistent with the report of Grumbach et al. (6). 2) Grumbach et al. examined the effect of 4PBA on ERp29 relative to CFTR trafficking in isolation, separate from the putative effects on ENaC insertion into the membrane. Because of the intimate relationship between CFTR and ENaC, it would be very interesting to examine the effect of 4PBA-restored ΔF508 CFTR on ENaC activity. It is important to examine putative causal relationships between 4PBA activation of ERp29 and ENaC activity, because in the CF lung, it would be undesirable to increase the rate of net salt and water reabsorption via ENaC, which would exacerbate the pulmonary condition stemming from excessively thick lung fluid. 3) ERp29 also serves as a connexin chaperone. There is emerging evidence that connexins can form functional hemichannels with detectable macroscopic current, although the biological significance of these hemichannels remains unclear. It is clear, however, that hemichannels can propagate calcium waves, which can certainly modulate ENaC and CFTR activity (1). 4) It would be of tremendous interest and value to extend these in vitro studies (primarily in MDCK and CFBE41o cells) to whole organism studies of the role of ERp29 in ENaC cleavage and activation.

REFERENCES