

Calisomerin: A Bifunctional ER Protein with Calcium Storage and Protein Disulfide Isomerase Functions

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The endoplasmic reticulum (ER) plays distinct regulatory roles by virtue of the proteins that reside within the lumen. High concentrations of calcium-binding proteins such as calsequestrin and calreticulin facilitate the storage of calcium ions, which are released into the cytosol in response to extracellular signals. Other luminal proteins, such as protein disulfide isomerase, mediate proper protein folding through catalysis of disulfide bonds. We identified a novel 432-amino acid residue human ER protein that serves both calcium storage and PDI functions and named it calisomerin. Calisomerin is found in animal cells but not in yeast or higher plant cells. It has an ER retention signal (KDEL-COOH) and three thioredoxin-like domains, each containing a WCXXC motif. In HeLa cells, calisomerin is almost as abundant as calreticulin, the major ER calcium storage protein in non-muscle cells. Calisomerin has a high proportion of acidic amino acids and calorimetric experiments demonstrated its capacity to bind calcium. Recombinant calisomerin exhibited PDI activity when tested using insulin as substrate. RNA interference was used to reduce calisomerin levels to < 30% in HeLa and Jurkat T cells, resulting in drastically reduced calcium responses to thapsigargin, caged-Ins 1,4,5-P₃, and various agonists known to mobilize intracellular calcium through Ins 1,4,5-P₃ production. [Ca²⁺]_{ER} in the siRNA-treated cells was ~ 30% that in control cells. Thus, the attenuated calcium responses in these cells were likely due to decreased calcium storage capacity of the ER. The Ca²⁺ responses were restored by expression of calisomerin in the siRNA-treated cells. The depletion of calisomerin also caused an accumulation of cell surface proteins in the ER, probably because of diminished PDI activity in the ER. These results suggest that calisomerin is a bifunctional protein that contributes to calcium homeostasis and protein folding in the ER.