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Secretory Pathway Stress Responses as Possible Mechanisms of Disease Involving Golgi Ca^{2+} Pump Dysfunction

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Abstract

In mammalian tissues, uptake of Ca^{2+} and Mn^{2+} by Golgi membranes is mediated by the secretory pathway Ca^{2+}- ATPases, SPCA1 and SPCA2, encoded by the *ATP2C1* and *ATP2C2* genes. Loss of one copy of the *ATP2C1* gene, which causes SPCA1 haploinsufficiency, leads to squamous cell tumors of keratinized epithelia in mice and to Hailey-Hailey Disease, an acantholytic skin disease, in humans. Although the disease phenotypes resulting from SPCA1 haploinsufficiency in mice and humans are quite different, each species-specific phenotype is remarkably similar to those arising as a result of null mutations in one copy of the *ATP2A2* gene, encoding SERCA2, the endoplasmic reticulum (ER) Ca^{2+} pump. SERCA2 haploinsufficiency, like SPCA1 haploinsufficiency, causes squamous cell tumors in mice and Darier's Disease, also an acantholytic skin disease, in humans. The phenotypic similarities between SPCA1 and SERCA2 haploinsufficiency in the two species, and the general functions of the two pumps in consecutive compartments of the secretory pathway, suggest that the underlying disease mechanisms are similar. In this review we discuss evidence supporting the view that chronic Golgi stress and/or ER stress resulting from Ca^{2+} pump haploinsufficiencies leads to activation of cellular stress responses in keratinocytes, with the predominance of pro-apoptotic pathways (though not necessarily apoptosis itself) leading to acantholytic skin disease in humans and the predominance of pro-survival pathways leading to tumors in mice.

Keywords

secretory pathway stress; Golgi stress; endoplasmic reticulum stress; acantholysis; Darier disease; cornification; unfolded protein response

1. Introduction

Maintenance of the appropriate concentrations of both cytosolic Ca^{2+} and luminal Ca^{2+} in secretory pathway organelles of mammalian cells requires the activities of three subfamilies of P-type Ca^{2+}-transporting ATPases. These are the sarco(endo)plasmic Ca^{2+}-ATPases (SERCA1-3; gene symbols *ATP2A1-A3*), the plasma membrane Ca^{2+}-ATPases (PMCA1-4; *ATP2B1-B4*), and the Golgi or secretory pathway Ca^{2+}-ATPases (SPCA1 and 2; *ATP2C1* and *ATP2C2*). The structures, biochemical characteristics, and physiological functions of the SERCA and PMCA pumps have been reviewed extensively [1-4] and will not be

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discussed in this review. The focus here is on the SPCA family of Golgi Ca^{2+} pumps, with particular emphasis on disease phenotypes resulting from null mutations in the *ATP2C1* (SPCA1) gene in mice and humans and their similarities to disease phenotypes resulting from null mutations in the *ATP2A2* gene, which encodes SERCA2, the major endoplasmic reticulum (ER) Ca^{+} pump.

Null mutations in a single copy of the *ATP2C1* or *ATP2A2* genes have been shown to cause autosomal dominant skin diseases (Hailey-Hailey disease (HHD) and Darier's disease (DD), respectively) in humans [5-7] and squamous cell tumors of keratinized epithelial cells in mice [8-11]. Although the phenotypes in humans and mice are very different, the primary genetic defect in each case leads to a reduction in the levels of functional Ca^{2+} pump in a compartment of the secretory pathway, and within each species the disease phenotypes are quite similar and involve keratinized epithelium. In this review we provide brief information about the identities and functions of the Golgi Ca^{2+} pumps, which have been reviewed by other investigators [1,12-15], and discuss evidence that secretory pathway stress, originating in either the Golgi or ER, and subsequent activation of Golgi and ER stress response pathways might serve as a common mechanism in the diseases resulting from Golgi or ER Ca^{2+} pump dysfunction.

2. The Golgi Ca^{2+} pump in yeast and mammals

The existence of a Golgi Ca^{2+} pump was first shown in biochemical studies of Golgi membranes from lactating bovine, rat, and mouse mammary glands. These included ATP-dependent Ca^{2+}-uptake into purified Golgi vesicles [16-19], inhibition of Ca^{2+}-ATPase activity and Ca^{2+}-uptake by orthovanadate [19], and identification of a 100-kilodalton phosphorylated intermediate [17]. The Ca^{2+} affinity of the Golgi enzyme differed from that of the sarcoplasmic reticulum Ca^{2+} pump and the plasma membrane Ca^{2+} pump and, unlike the latter enzymes, it was not inhibited by quercetin [20]. These observations provided strong evidence for a Golgi P-type Ca^{2+}-ATPase that was different from the SERCA and PMCA Ca^{2+} pumps.

The first molecular identification of the Golgi Ca^{2+} pump occurred in 1989 with the cloning of a putative yeast secretory pathway Ca^{2+} pump, termed PMR1 [21]. This was followed several years later by the cloning of a rat cDNA encoding a P-type ATPase, now termed SPCA1, which exhibited sufficient similarity to PMR1 to be considered its mammalian ortholog [22]. Later studies identified human [5,6] and C. elegans [23] SPCA1 orthologs and a second mammalian SPCA isoform, termed SPCA2 [24,25], and demonstrated that PMR1, SPCA1, and SPCA2 are expressed in Golgi membranes and function as Ca^{2+}- and Mn^{2+}-transporting ATPases [24-28]. Both SPCA1 and SPCA2 are expressed in lactating mammary glands [29,30] and SPCA2 is strongly induced during lactation [29], suggesting that the Golgi Ca^{2+} pump identified in the earlier studies of mammary glands [16-20] was a mixture of the two isoforms.

The presence of SPCA homologs in both higher and lower eukaryotes and the high degree of similarity to PacL, a bacterial Ca^{2+} pump [31], suggests that they have more ancient evolutionary origins than the SERCA and PMCA pumps. In plants, however, an SPCA homolog has not been identified, and the ECA3 Ca^{2+} pump, which is closely related to the SERCA pumps, is expressed in Golgi membranes and affects both Ca^{2+} and Mn^{2+} homeostasis [32]. The expression of a SERCA-like pump in plant Golgi membranes is consistent with evidence that, in addition to SPCA pumps, a thapsigargin-sensitive pump, presumably SERCA2, also contributes to Golgi Ca^{2+} stores in mammalian cells [28,33].

3. Cellular phenotypes resulting from knockdown or ablation of SPCA expression are consistent with secretory pathway stress and activation of stress responses

SPCAs from yeast, C. elegans, and mammals serve as Ca^{2+} and Mn^{2+} transporting ATPases in Golgi membranes [23,25,34-37] and thus function in maintaining the appropriate luminal Ca^{2+} and Mn^{2+} concentrations in this compartment of the secretory pathway. As discussed in this and the following section, ablation or reduction in SPCA activity causes Golgi dysfunction and stress, which in turn leads to activation of secretory pathway stress responses that appear to involve both survival and apoptotic mechanisms (summarized in Table 1).

In yeast, loss of PMR1 leads to glycosylation defects, impaired protein trafficking, and defective degradation of misfolded ER proteins [38]. In addition, absence of PMR1 causes growth inhibition and impairs proteolytic processing of α-factor, which is due at least in part to a reduction in the activity a Ca^{2+}-dependent Golgi protease [26,38]. Both growth inhibition and the defect in proteolytic processing are partially suppressed by increasing the Ca^{2+} concentration of the medium [38]. These findings and the observation that expression of SERCA1, the rabbit skeletal muscle Ca^{2+} pump, can alleviate growth inhibition of *pmr1* mutants [26] indicate that some of these phenotypes are due to a reduction of Ca^{2+} in the lumen of the Golgi. Mutations in PMR1 also lead to accumulation of cytosolic Mn^{2+} and cause hypersensitivity to Mn^{2+} toxicity [39], consistent with the suggestion that SPCAs function in Mn^{2+} detoxification [24], and increasing Mn^{2+} in the medium reverses defects in both N-linked and O-linked glycosylation [26]. These studies showed that the yeast SPCA homolog plays an important role in both Ca^{2+} and Mn^{2+} homeostasis in the Golgi apparatus, with primary effects on protein processing and trafficking.

Studies using keratinocytes from HHD patients have shown that loss of one copy of the SPCA1 gene (*ATP2C1*), which reduces SPCA1 expression to almost half of normal levels, causes a reduction in both the rate of Ca^{2+} sequestration and the levels of Ca^{2+} in Golgi vesicles [27], thus confirming a direct role for SPCA1 in maintaining Golgi Ca^{2+} stores in mammalian cells. Knockdown of SPCA1 expression in HeLa cells using RNA interference showed that SPCA1 mediates Ca^{2+} uptake in the Golgi, but also indicated that additional uptake is mediated by a SERCA pump [28]. Recent experiments confirmed these findings and showed that SPCA1 is expressed in the trans-Golgi compartment [37], consistent with earlier results [27]. More precise localization by immunogold labeling showed that SPCA1 is expressed in tubular parts of the trans-Golgi network and in tubular non-compact zones connecting the Golgi stacks, but little expression was observed in the cisternae [40]. RNA-interference experiments demonstrated that loss of SPCA1 affects both N-linked glycosylation [41] and trafficking of proteins through the secretory pathway [37,40,42].

In addition to maintenance of intra-Golgi Ca^{2+} and Mn^{2+}, which has direct effects on Ca^{2+}-dependent proteases [38] and Mn^{2+}-dependent glycosyltransferases [43], there is also evidence that SPCA1 may affect cytosolic Ca^{2+} signaling [44-48]. A particularly interesting observation is that Ca^{2+} released from the Golgi leads to a localized increase in cytosolic Ca^{2+} that stimulates vesicle fusion, thus contributing to intra-Golgi transport of cargo [49], a finding that is consistent with the distribution of SPCA1 in the Golgi apparatus [40]. Thus, maintenance of luminal Ca^{2+} stores by SPCA1 may enable Ca^{2+} signaling events that directly affect vesicle trafficking and associated sorting of proteins through the secretory pathway. If so, then a deficiency in this signaling function likely contributes to the mislocalization of proteins that occurs in response to SPCA1 knockdown [37,41,42].

SPCA (PMR1) deficiency in yeast affects not only the Golgi, but also the ER, where it has a clear effect on ER stress responses. In yeast, PMR1 was shown to be identical to DER5, a gene involved in ER-associated protein degradation (ERAD) of misfolded proteins, and *pmr1* mutants failed to efficiently degrade a mutant form of carboxypeptidase Y via the ubiqitin-proteosome pathway, apparently due to a failure in exporting the misfolded protein from the ER to the cytosol [26]. Null mutants were also more sensitive to treatment with dithiothreitol and tunicamycin [26], which cause ER stress due to accumulation of misfolded proteins in the ER, with subsequent activation of the unfolded protein response (UPR). Because both ERAD and the UPR are major components of the ER stress response, these findings suggest that loss of PMR1 activity in the Golgi can cause or exacerbate stress occurring in the ER, an earlier compartment of the secretory pathway, and impair the ability of the cell to adapt to ER stress.

Effects on the ER were also observed in mammalian cells. Knockdown of SPCA1 affected degradation of a mutant glycoprotein via ERAD, although it did not affect degradation of a non-glycoprotein substrate [41]. Signaling pathways that mediate ER stress responses were intact and functional; however, SPCA1-deficient cells were highly sensitive to treatment with tunicamycin or thapsigargin, both of which cause ER stress and activate ER stress responses [41]. The embryonic phenotype discussed below provides direct evidence of Golgi stress, secondary effects on the ER, and stress responses that can be categorized as survival responses or apoptotic responses.

4. Embryonic phenotypes resulting from ablation of SPCA1 and evidence of Golgi stress and activation of Golgi stress responses

Mouse embryos lacking SPCA1 appeared normal on embryonic day (ED) 8.5, but growth retardation and failure of neural tube closure were observed on ED 9.5 and embryolethality occurred between EDs 10 and 11 [11]. Loss of proteins involved in basic cellular functions often cause embryonic death around the time of implantation [50]; however, SPCA1-null embryos underwent blastocyst formation, implantation, development of the three germ layers, gastrulation, and major phases of organogenesis. This suggested that processing and trafficking of proteins through the secretory pathway, required for elaboration of cell surface proteins and secretion of extracellular matrix and signaling proteins, were relatively normal.

Some of the most common causes of embryolethality during the period in which SPCA1-null embryos died involve defects in hematopoiesis or the cardiovascular system [50]. However, red blood cells, the yolk sac, blood vessels, and heart appeared normal and supported circulation of blood [11]. The only structural defect was incomplete closure of the neural tube; however, bending occurred at dorsolateral and medial hinge points, suggesting that secretion of signaling factors required for neural plate bending [51] was occurring. Neural tube defects have a diversity of causes, including dysregulation of cell proliferation and/or apoptosis [52]. No reduction in mitotic index was observed; however, SPCA1-null embryos exhibited a significant increase in apoptosis in the neural tube and mesenchyme [11], suggesting that apoptosis was a major factor in both the neural tube defect and embryonic death. Increased apoptosis was also observed in neuronal cells subjected to RNA-mediated knockdown of SPCA1 in culture [42].

At the ultrastructural level, there were no apparent changes in desmosomes, junctional complexes, coated pits, mitochondria, or basement membranes [11]. This indicated that loss of SPCA1 either did not cause a massive perturbation of processing and trafficking of proteins in the secretory pathway or that compensation was occurring. SPCA1 mRNA was detected on ED 8.5, but not SPCA2 mRNA, suggesting that compensation for the loss of SPCA1-mediated Ca^{2+} uptake was due to other mechanisms. These may include the activity

of a SERCA pump, which contributes to Golgi Ca^{2+} handling [28,33], to partial filling of Golgi Ca^{2+} stores by fusion with vesicles containing Ca^{2+} from the ER, and/or to additional adaptations in the Golgi, discussed below. Regarding the role of SPCA1 in uptake of Mn^{2+} required for glycosyltransferases [43], inositol 1,4,5-trisphosphate receptors are present in both ER and Golgi [53] and can mediate uptake of Mn^{2+} [54]. This alternative Mn^{2+} uptake route may be sufficient during embryogenesis.

The most striking ultrastructural changes in SPCA1-null embryos involved the Golgi and provided clear evidence of Golgi stress. These included dilation of Golgi membranes, a reduction in the number of flat cisternae, an increase in the number of Golgi-associated vesicles, and other changes [11]. Although well-formed Golgi were occasionally observed (Fig. 1, left), they had fewer flat cisternae and a larger number of associated vesicles at the ends of the cisternae. The latter observation supports the suggestion [40,49] that Ca^{2+} release from Golgi stores served by SPCA1 contributes to membrane fusion. Dilated Golgi membranes were commonly observed (Fig. 1). Dilation of the rough ER, an indication of ER stress [55], and a reduction in the number of membrane-bound ribosomes, an indication of reduced ER-associated protein synthesis that is part of the ER stress response [56], were also observed (Fig. 1, middle). An additional indication of Golgi stress was the accumulation of excess lipid droplets in SPCA1-null cells [11]. This has also been observed in ATF6α knockout mice, where it was attributed to ER stress [57].

Given the critical role of the Golgi in the secretory pathway and both anterograde and retrograde trafficking between the ER and the Golgi, one would expect Golgi stress to affect the ER and to activate Golgi stress responses to deal with the perturbation. In fact, Golgi membranes were increased ~4-5 fold in SPCA1-null embryos [11], which should increase the capacity for processing and trafficking of proteins, and may be the major compensatory mechanism that allows embryonic development through EDs 10 and 11. Dilation and expansion of the amount of Golgi membranes were also observed in Tangier disease [58]. Like the ER, the Golgi appears to function in stress-sensing and to exhibit stress responses that allow a cell to either adapt to conditions causing insufficiency of Golgi function or undergo apoptosis [59-60]. Expansion of Golgi membranes is presumably part of a Golgi stress response, as it seems analogous to expansion of the ER, which occurs in response to ER stress (reviewed in 60-61). Expansion of the Golgi in SPCA1-null embryos, along with the induction of genes encoding Golgi proteins by XBP1 [62], an established regulator of ER biogenesis [63] that also causes expansion of the Golgi [64], suggest the existence of homeostatic mechanisms that adjust the amount of Golgi membranes to the needs of the cell, whether in response to Golgi stress or normal differentiation.

5. Haploinsufficiency of either SPCA1 or SERCA2 causes acantholytic skin disease in humans and squamous cell tumors in mice

Heterozygous loss-of-function mutations in SPCA1 cause HHD in humans [5,6] and squamous cell tumors in mice [11]. The phenotypes in both species are remarkably similar to those caused by loss-of-function mutations in a single copy of the SERCA2 gene, with DD in humans [7] and squamous cell tumors in mice [8,9]. In each case the genetic lesion is an autosomal dominant mutation of a P-type ATPase that sequesters Ca^{2+} in a compartment of the secretory pathway (Golgi or ER), and the only known target cell is the keratinocyte.

The most prominent characteristic of both HHD and DD, as discussed in numerous reviews [14,65-68], is the disruption of cell-cell contacts (acantholysis) in the suprabasal layer of the skin, which results from loss of desmosomal connections between cells. Ultrastructural studies of HHD [69] indicated that desmosomes and their connections with tonofilaments (keratin intermediate filaments) formed normally in non-lesional skin; however, in affected

cells, tonofilaments separated from the desmosomes, followed by clumping of tonofilaments, loss of desmosomes, and acantholysis [69]. A similar study of DD patients indicated that the morphological changes in the suprabasal layer were similar to those of HHD and suggested that the loss of connection between tonofilaments and desmosomes preceded the loss of desmosomes [70,71]. This view has been supported by other investigators [72-74], although there are counterviews [75,76], and non-lesional skin of HHD patients is more fragile [76], indicating that the process of acantholysis is not identical in the two diseases.

Squamous cell tumors, but not acantholytic skin diseases, were observed in SPCA1 and SERCA2 heterozygous mice. In the SERCA2 model, ~90% of the mice developed one or more squamous cell carcinomas or papillomas of the forestomach, oral mucosa, esophagus, or skin [8-10]. The wild-type allele was retained in the tumors, indicating that SERCA2 does not serve as a classical tumor suppressor and that haploinsufficiency is sufficient to cause cancer [9]. Sharp upregulation of H-ras and K-ras, with no apparent mutations, was part of the tumor mechanism. Upregulation of p53 was also observed and was proposed to slow tumor growth as loss of p53 resulted in growth of a massive tumor [9]. Similar tumors were observed in SPCA1 heterozygous mice (Fig. 2), but the incidence was lower (25%) [11]. The mechanisms have not been analyzed but are unlikely to involve loss of heterozygosity since the average age of onset was almost two years. The occurrence of tumors in SPCA1 heterozygous mice is consistent with the possibility that four cases of squamous cell tumors of the vulva in humans with HHD [77 and references therein] may be due to SPCA1 haploinsufficiency. Rare occurrances of squamous cell tumors have also been observed in DD [78 and references therein], and down-regulation of SERCA2 has been reported in human oral squamous cell tumors [79].

There has been a great deal of investigation and speculation about the underlying mechanisms of HHD and DD [reviewed in 14, 65-68], but there is currently no consensus. Defects in Ca^{2+} signaling or defective folding, processing, and trafficking of cell adhesion proteins have been proposed, but there is little evidence that the Ca^{2+} signaling functions of SPCA1 and SERCA2 are similar, and production and assembly of desmosomes appears normal in HHD keratinocytes [80]. Several investigators have discussed the possibility that Golgi stress or ER stress might be involved in HHD [11] and DD [65,67,81], respectively.

6. Secretory pathway stress and stress responses as potential common factors in disease caused by SPCA1 and SERCA2 haploinsufficiency in humans and mice

Secretory pathway stress originating in the ER and activation of ER stress responses are major mechanisms in a wide range of diseases [82-84]. These include neurodegenerative diseases [85,86], cardiovascular disease [87,88], diabetes [89], obesity [90], inflammatory bowel disease [91], kidney disease [92], chronic obstructive pulmonary disease [93], skeletal disorders [94], and cancer [95,96]. Any of a number of perturbations of ER function elicits a complex set of ER stress responses involving activation of signaling pathways that can lead to correction of the deficit, thus favoring survival, and activation of pathways that can, under certain circumstances, lead to apoptosis [97]. In the initial stages of ER stress, pathways favoring both survival and apoptosis are activated, but if the cell is able to adapt, then pro-apoptotic pathways diminish and the execution phase of apoptosis is avoided [98Rutkowski06].

One of the most common experimental methods to induce ER stress is to inhibit SERCA2 with thapsigargin, an effect seen at even very low levels [98]. Thus, a reduction in SERCA2

activity in differentiating keratinocytes has the potential to cause ER stress and elicit ER stress responses [65,67,81]. Indeed, if ER function is affected by reduced sequestration of Ca^{2+} by SERCA2, then ER stress response pathways would be activated to at least some degree in keratinocytes of DD patients and SERCA2 heterozygous mice. Although less well understood, Golgi stress [59,60,99], such as that occurring in SPCA1 null embryos [11], also elicits stress responses (Table 1 and section 3). Furthermore, ~50% knockdown of SPCA1 in HeLa cells, comparable to the reduction in SPCA1 in HHD keratinocytes that reduces luminal Ca^{2+} [27], led to fragmentation of the Golgi and other indications of Golgi stress [37]. Thus, haploinsufficiency of both SERCA2 and SPCA1 causes secretory pathway stress, which in turn would be expected to activate stress response pathways that lead to survival or apoptosis.

The role of ER stress and related adaptive stress responses, such as the UPR, in cancer are well established and result from activation of survival pathways and suppression of apoptotic pathways [95,96]. The absence of ras and p53 mutations in tumors of SERCA2 heterozygous mice suggested a novel mechanism involving a global change in tumorigenic potential of the keratinized epithelium [9], which would be consistent with chronic ER stress and activation of survival responses favoring tumorigenesis. The Golgi is also involved in stress sensing and can mount stress responses that affect tumorigenesis [100]. For example, polo-like kinase 3 is involved in Golgi fragmentation during mitosis and apoptosis and functions as a tumor suppressor [100]. If survival responses to secretory pathway stress in mouse keratinocytes, originating in either the ER or Golgi, are favored over apoptotic responses, then these stress responses could be part of the mechanism of tumorigenesis in SERCA2 and SPCA1 mutant mice and in the few squamous cell tumors in HHD [77] and DD [78] patients.

As in many other diseases [82-96], chronic secretory pathway stress and activation of stress responses could be also part of the underlying mechanisms of HHD and DD. Acantholytic skin disease in humans is quite different from the phenotype of squamous cell tumors in mice; however, because ER stress leads to activation of pathways favoring either adaptation or apoptosis, it is possible that differences in the balance between these stress responses in mouse and human keratinocytes account for the differences in phenotype.

Manifestations of HHD and DD first occur in suprabasal keratinocytes as they begin differentiation. Keratinocyte differentiation involves i) the synthesis and trafficking of structural proteins, enzymes, and lipids needed to form the mature corneocyte and ii) a novel form of programmed cell death [101-103]. The UPR, a component of the ER stress response, regulates transcriptional programs that expand the secretory pathway [104] and plays a role in the differentiation of a number of cell types [105,106], including human epidermal keratinocytes [107]. ER or Golgi Ca^{2+} pump dysfunction causes secretory pathway stress and could therefore interfere with normal utilization of the stress response pathways during differentiation of keratinocytes. If there were insufficient reserve for adaptive stress responses, then apoptotic responses might be favored. Even if apoptotic stimuli did not reach a threshold sufficient for the execution phase, they could interfere with the specialized process of programmed cell death in keratinocytes [101-103], which must occur properly if the cell is to become a functional, but non-living corneocyte. Caspases involved in apoptosis contribute to cornification [108-109] and desmosomal proteins are particularly susceptible to cleavage during apoptosis [110-111].

Interestingly, desmoplakin, the desmosomal component to which keratin intermediate filaments attach, is cleaved efficiently by caspase 2 [111], an initiator caspase localized to the Golgi. Finally, there is evidence that apoptosis occurs in lesional tissue of both DD and

HHD patients [112] and the reduced expression of the anti-apoptotic proteins Bcl-2 and Bcl-x_L in DD lesions [113] is consistent with activation of apoptotic responses in this disease.

7. Concluding remarks

The studies discussed in this review have shown that haploinsufficiency of either SPCA1 or SERCA2 causes acantholytic skin disease in humans and squamous cell tumors in mice. Both Ca^{2+} pumps serve in a compartment of the secretory pathway; keratinocytes are the affected cell type in both species; and dysfunction involving either pump leads to secretory pathway stress and elicits secretory pathway stress responses. These commonalities suggest that the underlying disease mechanisms are similar and, like so many other diseases [82-96], involve secretory pathway stress and activation of powerful stress response signaling pathways. These pathways contribute to either adaptation and cell survival or to apoptosis and cell death. Differential activities of prosurvival or proapoptotic arms of the stress response pathways in human and mouse keratinocytes may be the basis of the dramatic species differences in disease phenotypes.

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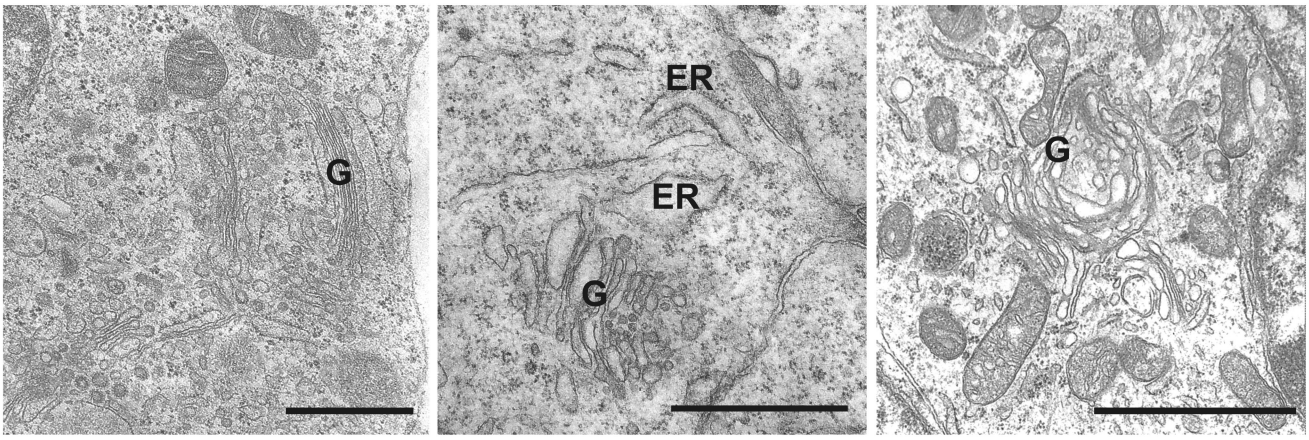

Fig. 1.

Golgi stress and Golgi stress responses in SPCA1-null embryos. Ultrastructural analysis revealed occasional examples of Golgi (G) with well-formed flattened stacks (left), but the number of cisternae were significantly reduced and the total amount of Golgi membranes and associated vesicles were significantly expanded (see morphometry in Ref. 11). Dilation of Golgi membranes (middle and right) was commonly observed and dilated rough ER (middle) was also observed. Dilation of Golgi and ER are indicators of Golgi and ER stress, and expansion of the Golgi is an apparent stress response favoring adaptation and survival (11). Bar = 1 micrometer

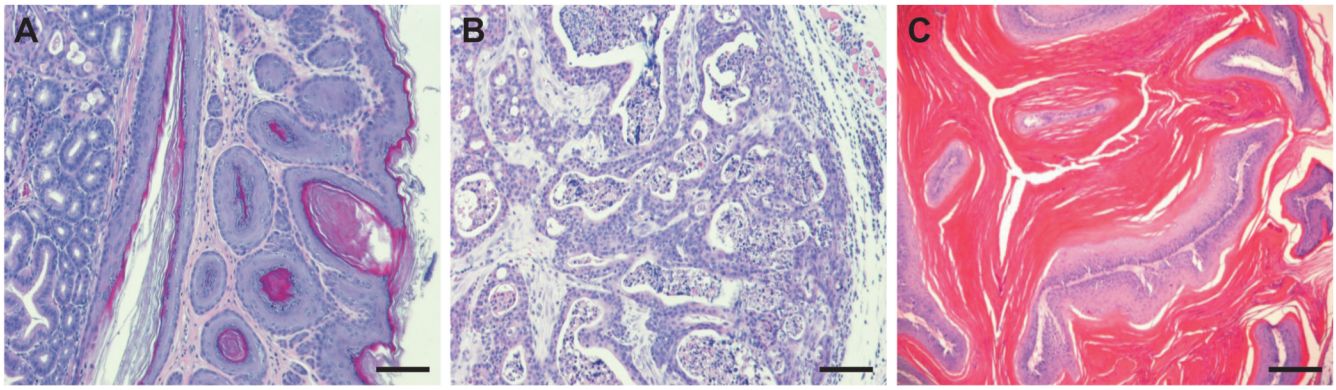

Fig. 2.

Squamous cell tumors in SPCA1 heterozygous mice. Carcinomas and papillomas were observed in keratinized epithelia of SPCA1 heterozygous mice (11), but the incidence was lower and the age of onset later than in SERCA2 heterozygous mice (8,9). **A,** Moderate hyperplasia of the forestomach in a 23-month-old heterozygous male; this phenotype was rarely observed in SPCA1 heterozygous mice, but was invariably observed in forestomach of SERCA2 heterozygous mice by 3 months of age. **B,** Poorly differentiated skin carcinoma in 22-month-old heterozygous male. **C,** Papilloma with severe hyperkeratosis from peri-anal region of 22-month-old heterozygous male. Bar = 100 micrometers in A and B, 200 micrometers in C.

Table 1

Phenotypes resulting from SPCA-deficiency that are indicative of secretory pathway stress and activation of stress responses secondary to defective Ca^{2+} and Mn^{2+} sequestration

I. Manifestations of secretory pathway (Golgi or ER) stress.	**References**
1. Defective glycosylation, likely due to Mn^{2+} deficiency in Golgi	21,26,38,41
2. Impaired proteolytic processing of proteins in Golgi, likely due to Ca^{2+} deficiency	26, 38
3. Impaired trafficking of proteins in secretory pathway	21,37,38,40-42
4. Impaired ERAD; selective for glycosylated substrate in mammalian cells	38,41
5. Increased sensitivity to ER stress caused by tunicamycin, dithiothreitol, or thapsigargin	26,41
6. Dilation of Golgi membranes and/or reduction in number of Golgi stacks	11,58
7. Disaggregation or fragmentation of Golgi membranes	11,37,40
8. Dilation of ER indicative of ER stress, secondary to Golgi stress	11
9. Accumulation of cytosolic lipid droplets	11,57
II. Manifestations of Golgi stress responses	
1. Increase in amount of Golgi membranes and Golgi-associated vesicles (survival response)	11,58
2. Increased apoptosis	11,42