Darier’s disease (DD), also known as keratosis follicularis, is an autosomal dominant skin disorder characterized by loss of adhesion between epidermal cells (acantholysis) and abnormal keratinization. DD is also associated with 18 U.S.C. Section 1734 solely to indicate this fact. The disease is characterized by clinical features of hyperkeratosis, papules, and plaques on the face, neck, and chest. The genetic basis of DD was discovered in 1958, when it was discovered that the mutations in the ATP2A2 gene encode the SERCA2b isoform of the sarcoplasmic reticulum Ca^{2+}-ATPase. Although >100 mutations in the ATP2A2 gene are known to cause DD, most mutations lead to a reduction in SERCA2b activity. These mutations have been reported to cause a diverse range of clinical manifestations, including skin disorders and neuropsychiatric disorders. Some mutations have been reported to cause severe skin disorders, while others have been associated with mild skin changes and isolated neuropsychiatric symptoms. However, the correlation between genotype and phenotype remains incomplete and, for the most part, relies on a single patient description of the disease for the vast majority of the mutants.

In this work, we analyzed 12 DD-associated mutations from all of the regions of SERCA2b to study the underlying pathologic mechanism of DD and to elucidate the role of dimerization in SERCA2b activity. Most mutations markedly affected protein expression, partially because of enhanced proteasome-mediated degradation. All of the mutants showed lower activity than the wild type pump. Notably, several mutants that cause relatively severe phenotypes of DD inhibited the activity of the endogenous and the co-expressed wild type SERCA2b. Importantly, these effects were not attributed to changes in passive Ca^{2+} leak, inositol 1,4,5-trisphosphate receptor activity, or sensitivity to inositol 1,4,5-trisphosphate. Rather, co-immunoprecipitation experiments showed that SERCA2b monomers interact to influence the activity of each other. These findings reveal multiple molecular mechanisms to account for the plethora of pathologic states observed in DD and provide the first evidence for the importance of SERCA2b dimerization in pump function in vivo.

Received for publication, February 14, 2003
Published, JBC Papers in Press, April 1, 2003, DOI 10.1074/jbc.M301638200

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of the native and of co-expressed WT pumps. These findings provide the first evidence to indicate physical and functional interaction between SERCA2b monomers. Although no definitive correlations between the mutations and DD phenotype became apparent, probably because of poor clinical information available for this disease, our findings do provide a molecular mechanism to account for the disease pathogenesis and how diverse phenotypes can be manifested.

**EXPERIMENTAL PROCEDURES**

**Materials, Antibodies, and Solutions**—Chelex, ATP, phosphoraceticine, creatinine phosphokinase, antimycin A, and oligomycin were purchased from Sigma. Fluoro-3-pentaammonium salt was from Molecular Probes, Inc. (Eugene, OR). N-Myo-inositol 1,4,5-triphosphate (IP$_3$) hexaammonium salt was from Alexis Biochemicals (San Diego, CA). Streptolysin O was from BD Diagnostic Systems (Sparks, MD). Lactacystin and ionomycin were from Calbiochem. Fetal bovine serum and 0.05% trypsin/EDTA were from ATLANTA Biologicals (Norcross, GA). Restriction enzymes were obtained from New England Biolabs (Beverly, MA) and Roche Applied Sciences.

**Cell Culture and Transfection**—HEK 293 cells were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal calf serum. The SERCA constructs were transfected using LipofectAMINE reagent (Invitrogen). The cells were used for immunoprecipitation or immunoblotting 48 h after transfection.

**Site-directed Mutagenesis**—The pcDNA3.1 plasmid containing human SERCA2b was a generous gift from Dr. Jonathan Lytton (University of Calgary, Calgary, Canada). Site-directed mutagenesis was performed using the QuikChange site-directed mutagenesis kit from Stratagene (La Jolla, CA) according to instructions provided by the manufacturer. All of the mutations were verified by the sequencing of four separate clones from each mutant. The mutants generated for this work are listed in Table I.

**Preparation of HA-tagged and Myc-tagged Human SERCA2b Constructs**—HA- and Myc-tagged human SERCA2b constructs were generated by PCR amplification of human SERCA2b using the 5’-oligonucleotide primer 5’-AC GTC AAT GGG TCG ACT ATT TAC G-3’ containing the underlined SalI and 3’-oligonucleotide primer 5’-AGA AGG CAC AGT CGA GGC TG-3’ located after a NotI site. The amplified DNA was gel-purified, digested with appropriate enzymes, and ligated into the pcMV-HA or Myc vectors (Clontech Laboratories, Inc., Palo Alto) that had been digested with SalI and NotI and gel-purified. The constructs were verified by DNA sequencing.

**Immunoprecipitation and Immunoblotting**—Transfected HEK 293 cells were washed with phosphate-buffered saline and lysed with buffer containing 135 mM NaCl, 0.1% Triton X-100, 20 mM Tris-HCl, pH 7.4, and a protease inhibitor mixture (Roche Applied Sciences). Precleared lysates (up to 500 μg of protein) were mixed with 3 μl of anti-HA antibodies or anti-Myc antibodies and incubated for 2 h at 4 °C in lysis buffer. Immune complexes were collected by overnight incubation with 50 μl of protein G-Sepharose at 4 °C under gentle agitation. Immunoprecipitated proteins were washed four times with lysis buffer prior to electrophoresis. The immunoprecipitates or lysates were suspended in SDS sample buffer and separated by SDS-polyacrylamide gels. After transfer to nitrocellulose membranes, the proteins were visualized using the enhanced chemiluminescence detection system (Amersham). The proteins were quantified by densitometry.

**Protein Levels of SERCA2b Mutants**—Because haploinsufficiency cannot explain the variable phenotype of DD patients (12), our initial hypothesis was that the severity of the disease may correlate with protein expression levels. This hypothesis was refuted by the finding that most DD mutants examined affected SERCA2b expression and/or stability (Fig. 1A). With the exception of two mutants (C344Y and V843F), all of the mutants markedly reduced protein expression. The possibility of variable SERCA2b expression because of variable transfection efficiency was excluded by the analysis of co-transfected green fluorescent protein (Fig. 1B).

Effect of the N-terminal mutants is consistent with previous work with SERCA1. Deletion of the N-terminal domain of SERCA1 reduced protein expression (13). Accordingly, mutation of SERCA2b Asn-39 to Asp or Thr reduced protein expression, suggesting that the integrity of the N terminus is important for pump expression. Interestingly, all of the truncation mutants including E917X markedly reduced protein expression, suggesting increased degradation of these pump products (see below). No concrete conclusion emerged from the other mutations. Thus, a mutation in the P domain (phosphorylation domain), C334Y, had minimal effect on protein expression, whereas another mutation, F487S, markedly reduced protein expression. Similarly, G769R in TM5 reduced protein expression, whereas V843F in the TM8-TM9 loop had minimal effect. Hence, the overall significance of the protein expression findings to DD is that the mutations can affect pump activity by multiple mechanisms. Some mutants affect pump activity because of reduced protein expression, whereas others such as C344Y and V843F must act by a different mechanism. The results in Fig. 1 together with the phenotypic information listed in Table I indicate a lack of correlation between protein expression and disease phenotype.

**Proteasome-mediated Degradation of Mutant SERCA2b Protein**—Previous work showed that lactacystin, a specific proteasome inhibitor, enhanced degradation of WT SERCA1 and prevented the small degradation of AAla3-SERCA1 but had no effect on several other deletion or mutations between Glu2-AAla14-SERCA1 (14). Therefore, we tested the effects of lactacystin on SERCA2b protein levels. Several of the mutants that showed low protein expression exhibited enhanced protein degradation. However, as with protein expression, protein degradation followed a complex pattern with respect to the effect of individual mutants (Fig. 2). First, we confirmed the finding that...
made with SERCA1 by observing slight increased degradation of WT SERCA2b by lactacystin. Furthermore, lactacystin similarly increased degradation of the C344Y and V843F mutants that had minimal effect on protein expression. The group of mutants most susceptible to degradation by the proteasome is the nonsense and the premature translation termination codon-inducing frameshift mutations (1625delAG). Lactacystin increased the expression of these mutants between 5- and 10-fold (Fig. 2). Selective effect of lactacystin on the degradation of several SERCA2b mutants was determined 24 h later. The most interesting mutants were the 5 of the 12 tested (42%) (N39D, N39T, C344Y, F487S, and S920Y) that had no activity and did not affect Ca\(^{2+}\) pumping by the native pumps.

The most interesting results were obtained by measuring SERCA pump activity. Selective traces, the experimental protocols, and the parameters tested are illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3. A summary of pump activity of native cells, cells transfected with the WT pump, and all of the mutants is illustrated in Fig. 3.
tion of relevance to DD where the WT and most mutants mRNA are likely to be present at comparable levels. Therefore, to simulate the DD situation, a 1:1 mixture of WT and the mutant clones that reduced the activity of the native pump were transfected and the resulting pumping activity measured. The results are summarized in Fig. 5. The expression of WT SERCA2b again increased Ca$^{2+}$ pumping rate by ~3-fold, and this rate was taken as 100% control. Co-expression of WT and the G769R mutant that had no effect on the native pump (Fig. 4) was used as an expression control, and as expected, it had no effect on Ca$^{2+}$ pumping by the expressed WT SERCA2b. Fig. 5 shows that all of the mutants that reduced the activity of the native pump similarly inhibited the activity of the expressed WT SERCA2b, indicating that the inhibition is inheritant to these mutants.

The poor clinical definition of DD phenotype makes it difficult to draw a precise correlation between the mutants that inhibited WT SERCA2 activity and the disease phenotype. However, the tendency is that mutants that cause a relatively severe phenotype such as F487S and S920Y noticeably inhibited endogenous and expressed WT SERCA2b activity. The finding of reduced WT pump activity by the mutants provides the first molecular mechanism that can account for the variable DD phenotypes.

Passive Ca$^{2+}$ Leak and IP$_3$ Sensitivity—The next question we addressed is how the DD-associated mutations reduce WT SERCA2b-pumping activity. One possibility is that the mutant proteins increase passive Ca$^{2+}$ leak across the ER membrane, resulting in an apparent reduced pumping rate. Increased passive leak was proposed to account for the inhibition of native Ca$^{2+}$ pump activity by SERCA1 splice variants when expressed in heterogeneous systems (15). In this work, we used a SERCA pump inhibition protocol to estimate the Ca$^{2+}$ leak rate at the end of the uptake period. Measurement of Ca$^{2+}$ leak with all of the DD mutants used in this work (Fig. 3, D–F, BHQ addition) showed that this mechanism cannot account for the reduced

![Image 1](https://example.com/image1.png)

**Fig. 3. Ca$^{2+}$ uptake, IP$_3$-mediated Ca$^{2+}$ release and Ca$^{2+}$ leak in cells expressing WT and mutant SERCA2b.** Approximately 48 h after transfection, cells were released from culture plates and counted, and 3 x 10$^5$ cells were washed and added to permeabilization medium to measure Ca$^{2+}$ uptake into the ER as described under “Experimental Procedures.” The rate of Ca$^{2+}$ pumping was determined from the slopes of reduction in medium [Ca$^{2+}$]. Ca$^{2+}$ uptake was measured in control non-transfected HEK 293 cells (A and D) and cells transfected with F487S (B and E) and WT SERCA2b (C and F). At the end of Ca$^{2+}$ uptake, IP$_3$-mediated Ca$^{2+}$ release was measured by the addition of increasing concentrations of IP$_3$, at 0.15, 0.30, 0.45, and 2.95 μM (A–C) and the rate of Ca$^{2+}$ leak was determined by inhibiting the pump with 100 μM SERCA pump inhibitor BHQ (D–F). Residual stored Ca$^{2+}$ was released by the addition of 2 μM ionomycin (I) at the end of each experiment. All traces were calibrated as described under “Experimental Procedures.”

![Image 2](https://example.com/image2.png)

**Fig. 4. Ca$^{2+}$ transport by WT and mutant SERCA2b pumps.** The protocol of Fig. 3 was used to evaluate pump activity of all of the mutants. The number of experiments is given in the columns. The results are plotted as the mean ± S.E. * and #, statistically significant difference of $p < 0.05$ and $p < 0.01$, respectively, compared with control.

**Table: Mutant**

| Mutant | Activity (%) Control |
|--------|---------------------|
| Control | 100 ± 5             |
| WT     | 100 ± 5             |
| N39D   | 35 ± 5              |
| N39T   | 40 ± 5              |
| DL41   | 45 ± 5              |
| DH42   | 40 ± 5              |
| C344Y  | 30 ± 5              |
| F487S  | 40 ± 5              |
| K542X  | 30 ± 5              |
| G769R  | 20 ± 5              |
| Q790X  | 60 ± 5              |
| V843F  | 40 ± 5              |
| E917X  | 40 ± 5              |
| S920Y  | 20 ± 5              |

* * P<0.05 # P<0.01
SERCA pump activity, because none of the mutants increased the passive Ca\(^{2+}\) leak. Because SERCA pumps determine Ca\(^{2+}\) content in the ER and the ER Ca\(^{2+}\) load affect sensitivity to IP\(_3\) (5), another possibility is that the mutant pumps altered IP\(_3\) mediated Ca\(^{2+}\) release. The measurement of the extent of Ca\(^{2+}\) release and its dependence on IP\(_3\) concentration showed that none of the mutants had an apparent effect on IP\(_3\)-mediated Ca\(^{2+}\) release (Fig. 3, A–C), confirming the results obtained in the SERCA2b\(^{-/-}\) mice (7).

**Interaction between SERCA2b Monomers**—The simplest mechanism by which the mutants can inhibit the activity of the WT SERCA2b is reducing the expression of the pump; however, this was found not to be the case (Fig. 6). The level of WT pump protein was not affected by co-expression of any of the mutant proteins. Equally, co-expression of the WT and mutant pumps had no effect on expression of the mutant pumps.

A second alternative is that SERCA2b exists as a dimer and the mutants, including those that are expressed at low levels, interact with the WT pump to reduce its activity. A clue to this possible mechanism is provided by earlier work suggesting that SERCA pump monomers sense and are influenced by their neighbors. Thus, the titration of Ca\(^{2+}\)-ATPase and Ca\(^{2+}\) uptake activities with fluorescein isothiocyanate (16), radiation inactivation analysis of pump activity and integrity (17, 18), freeze-fracture and deep-etching of sarcoplasmic reticular membranes (19, 20), and analysis with photoaffinity spin-labeled derivative of ATP (21) all suggested that the functional unit of the Ca\(^{2+}\)-ATPase is a dimer. Furthermore, an analysis of a purified 48-kDa SERCA1 fusion protein by small angle x-ray scattering suggested a requirement of the hinge domain (amino acids 670–728) region for self-association of the large hydrophilic domain into a dimer (22). Thus, it is possible that the mutant pumps affect the WT pump by way of protein interaction.

To test interaction between pump monomers, we attempted to co-immunoprecipitate (co-IP) co-expressed HA- and Myc-tagged SERCA2b. Initial attempts to do so failed. Fig. 7, A and B, shows that when the cells were lysed with a medium containing 1.0% Triton X-100 and 150 mM NaCl, it was possible to immunoprecipitate each of the tagged monomers but not to co-IP them. We then considered the possibility that interaction among the SERCA2b monomers is subtle and could not withstand the harsh solubilization conditions. This was confirmed by observing co-IP of the monomers when the cells were lysed in a medium containing 0.1% Triton X-100 and 135 mM NaCl (Fig. 7, C and D). Furthermore, co-IP of the SERCA2b monomers could be observed when the cells were lysed with 1% of the milder detergent Nonidet P-40 (data not shown). The findings in Fig. 7 provide the first direct evidence that SERCA2b monomers can interact with each other in vivo.

The functional consequence of dimerization of the SERCA2b monomers can be deduced from examining the interaction of the mutants with the WT pump. The results of such analysis are displayed in Fig. 7, E and F. Several findings are noticeable. First, most but not all SERCA2b mutants interact with the WT pump, providing a plausible explanation for inhibition of the native and expressed WT SERCA2b activity by the mutants. Second, all of the extreme N-terminal mutants showed reduced co-IP compared with their expression levels, implicating this region of the protein in dimerization. The same probably holds for the G769R mutation that showed good expression when expressed alone (Fig. 1 and 2) or together with the WT pump (Fig. 6) but showed very poor co-IP (Fig. 7). Because this mutation inserts an additional positive charge into TM5, it may result in misfolding of the protein to prevent dimerization. Third, all of the truncation mutants and the S920Y mutant...
showed preferential co-IP with the WT pump, more than expected from their expression. Because the truncation mutants are the most susceptible to proteolysis (Fig. 3), the simplest explanation for this finding is that dimerization protects these mutants from proteolysis. However, the analysis of protein expression levels in Fig. 6 does not support such an explanation. Another possibility is that sequences C-terminal to position Glu-917 (the shortest truncation tested) function to reduce pump dimerization and their truncation resulted in enhanced association of the truncated mutants with the WT pump. This interpretation is supported by the finding that the only other mutation to induce preferential binding is the S920Y and that this portion of the protein between TM8 and the C terminus is the most susceptible to proteolysis (Fig. 3), the simplest explanation for this finding is that dimerization protects these mutants from proteolysis.

**DISCUSSION**

Ca$^{2+}$ pools have a key role in shaping the spatiotemporal complexity of Ca$^{2+}$ signaling and in controlling cellular processes of major physiological and pathological relevance (24). SERCA pumps are key participants in the Ca$^{2+}$ signal as they determine ER Ca$^{2+}$ content at rest and during stimulation (10). In addition, several ER functions such as the activity of several chaperones and that of the unfolded protein response are regulated by ER Ca$^{2+}$ content (25, 26). Thus, it is not surprising that mutations in SERCA2 pump activity lead to DD. However, DD is characterized by variable phenotypes from very mild symptoms with dislodging of skin keratinocytes to severe manifestations with several neurological deficiencies.

The effect of DD-causing mutations on SERCA2b pump activity is unknown, let alone the underlying mechanism for the variable phenotype of the disease. In this work, we analyzed several mutations that cause DD in an effort to partially address these questions and to gain a further understanding of SERCA2b pump function. All of the mutations analyzed with the exception of one showed no Ca$^{2+}$-pumping activity, and the V843F mutation reduced pump activity by 50%. Hence, it is clear that the mutations that cause DD do so by reducing SERCA2b activity. Multiple biochemical mechanisms appear responsible for reduced pump activity. Thus, nonsense mutations resulted in truncated pump proteins that were susceptible for degradation by the proteasome. Several missense mutations caused a marked reduction in protein levels that was partially attributed to degradation by the proteasome, whereas others had a minimal effect on pump expression. This variability probably contributes to the variable clinical phenotype, but it is not sufficient to account for all of the variability because 11 of the 12 mutants examined had no pumping activity.

The two most notable and related findings in this work are the biochemical evidence for interaction between SERCA2b monomers and the inhibition of the native and expressed WT SERCA2b activity by five of the mutants. The crystal structure of SERCA1 in the E1 (Ca$^{2+}$) (27) and E2 (2H) (23) conformations suggest that SERCA pumps can exist as monomers. Of course, this does not exclude the possibility that in vivo the monomers interact with each other or that the pump functions as a dimer. Indeed, several lines of functional and biochemical evidence (16–21) support this notion. Here we provided the first direct evidence that SERCA2b exists as a dimer by showing that HA-tagged and Myc-tagged pumps can be co-IPed under mild extraction conditions. Importantly, all of the DD mutants interacted with the WT pump.

The significance of interaction of the WT and mutant SERCA2b monomers in vivo is that it provides a mechanism to explain reduced Ca$^{2+}$ pumping below 50% that is expected from the recessive nature of the disease. This provides a likely mechanism to account for the variable clinical features of DD. Hence, the essential role of SERCA2b in Ca$^{2+}$ signaling makes it vital for life, and even a 50% reduction in pump activity is not tolerated, leading to the detachment of skin keratinocytes. Other cellular activities such as Ca$^{2+}$-dependent exocytosis (7) and myocytes contractility (28) undergo adaptation to the modified Ca$^{2+}$ response. However, the interaction of WT and the DD-causing mutants that leads to a further reduction of SERCA2b pump activity is likely to affect additional cells and organs such as the nervous system.

The clinical features of DD point to particular vulnerability of keratinocytes and neuronal cells to mutations in SERCA2b and Ca$^{2+}$ homeostasis in the ER. This suggests that a cellular function common to the two cell types is particularly sensitive to ER Ca$^{2+}$ content. Such a potential function can be cell-cell and cell-matrix attachment that in keratinocytes are mediated by cadherins, a family of calcium-dependent adherent proteins. Cadherins also play a central role in the formation of neuronal connections (29, 30) and may contribute to neurite outgrowth.
and pathfinding and to synaptic specificity in the central nervous system (31). Aberrant function of cadherins can explain the symptomatic skin disorders in DD and that the second most prevalent disorder in DD is neurological deficiencies. If aberrant function of cadherins is the underlying cause of DD symptoms, our findings point to a central role of ER Ca\(^{2+}\) in the function of cadherins.

Most studies attribute Ca\(^{2+}\) regulation of cadherins function to extracellular Ca\(^{2+}\) (32, 33). In fact, little is known regarding the role of [Ca\(^{2+}\)]\(_{\text{ER}}\), in the regulation of cadherins function. However, accumulating evidence points to such a role. Depletion of ER Ca\(^{2+}\) with thapsigargin and cyclopiazonic acid prevented accumulation of cadherins at cell-cell junctions (34) and increased endothelial permeability by increasing discontinuities in cadherins junctions (35). Conversely, increased ER Ca\(^{2+}\) load by overexpression of calreticulin, a Ca\(^{2+}\) storage protein and chaperone in the ER, enhances assembly of cadherins junctions in cell-cell contacts (36). Significantly, dissociation of cadherins was observed in the skin of patients with DD (37). Together, these findings point to the importance of ER Ca\(^{2+}\) in cadherins function and their possible aberrant function in DD.

In summary, this work demonstrates multiple effects of mutations in SERCA2b pump associated with DD. The mutations affect protein expression, degradation, and activity. The most significant finding is that several DD-associated mutants inhibit the activity of the native and the expressed WT pumps. The inhibition was not the result of altered protein expression nor increased passive leak but rather the inhibition of pumping activity by protein-protein interaction. These findings provide a plausible molecular mechanism for diverse phenotypes of DD and a framework to further understand the role of SERCA2b in specific cell functions.

Acknowledgment—We thank Dr. Jonathan Lytton (University of Calgary, Calgary, Canada) for generously providing the SERCA2b clone.

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SERCA2b and Darier’s Disease
Multiple Effects of SERCA2b Mutations Associated with Darier's Disease

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J. Biol. Chem. 2003, 278:20795-20801.
doi: 10.1074/jbc.M301638200 originally published online April 1, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M301638200

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