A Glutamine to Proline Exchange at Amino Acid Residue 1098 in Sucrase-isomaltase Causes a Temperature-sensitive Arrest of Sucrase-Isomaltase in the Endoplasmic Reticulum and cis-Golgi

Marcus J. Pröpsting, Ralf Jacob, and Hassan Y. Naim‡

From the Department of Physiological Chemistry, School of Veterinary Medicine, D-30559 Hannover, Germany

A striking feature of phenotype II in congenital sucrase-isomaltase deficiency is the retention of the brush border protein sucrase-isomaltase (SI) in the cis-Golgi. This transport block is the consequence of a glutamine to proline substitution at amino acid residue 1098 of the sucrase subunit. Here we provide unequivocal biochemical and confocal data to show that the SIQ/P mutant reveals characteristics of a temperature-sensitive mutant. Thus, correct folding, competent intracellular transport, and full enzymatic activity can be partially restored by expression of the mutant SIQ/P at the permissive temperature of 20 °C instead of 37 °C. The acquisition of normal trafficking and function appears to utilize several cycles of anterograde and retrograde steps between the endoplasmic reticulum and the Golgi implicating the molecular chaperones calnexin and heavy chain-binding protein. The data presented in this communication are to our knowledge the first to implicate a temperature-sensitive mutation in an intestinal enzyme deficiency or an intestinal disorder.

The molecular basis of many genetic diseases, severe or mild, is an abnormal or an altered protein folding that is associated with a loss in protein function, intracellular protein degradation, or impaired transport and missorting of the protein to a different organelle or membrane domain where it is not capable of exerting its correct function (for a review, see Ref. 1). Oftentimes a single point mutation or a deletion in the coding region of a gene is the underlying cause for the generation of the folding mutant. The mechanisms of folding and vesicular transport of proteins implicate structural elements in the protein itself and cellular protein components interacting with these structures (2). A complex cascade of association, dissociation, and reassociation dominates the life cycle of many proteins that transiently reside in the ER before their exit and further trafficking to their final destination at the cell surface, the Golgi apparatus, or the lysosomes (for a review, see Ref. 3). These bindings involve ER-resident proteins, molecular chaperones that retain proteins until they have acquired a correct conformation ultimately enabling them to leave the ER. For many proteins a transport-competent configuration is critically associated with homodimerization or formation of a multimeric complex comprising the diverse subunits of the protein. These steps are subject to a quality control mechanism that discriminates between proteins in terms of their folding pattern and permits correctly folded proteins to exit the ER. The majority of the naturally occurring mutants implicated in diseases cannot traverse the quality control machinery of the ER and are retained in that organelle (1). In a few cases of the intestinal disorder congenital sucrase-isomaltase deficiency (CSID), however, arrest of the protein in the trans-Golgi, cis-Golgi, and ERGIC compartments is reminiscent of escaping the ER quality control and suggests the existence of a quality control mechanism operating beyond the ER (4, 5). This hypothesis is supported by another example of a cell surface protein that is blocked beyond the ER (most likely in the cis-Golgi): the temperature-sensitive tsO45 mutant of the G protein of the vesicular stomatitis virus (6). This mutant form undergoes several cycles of anterograde and retrograde trafficking between the ER and the cis-Golgi at the permissive temperature before acquisition of a transport-competent configuration. It is not clear whether mutant forms of SI that are localized in the Golgi are causally temperature-sensitive and would follow a pattern of folding mechanisms similar to the G protein. Temperature-sensitive mutants are characterized by a drastic alteration in their folding and biological activity above a certain temperature, known as the non-permissive temperature. Below this temperature the structure and function is restored to similar levels as the wild type proteins. There are few examples of temperature-sensitive mutants of membrane proteins that are implicated in diseases. One known temperature-sensitive mutant phenotype is the deletion mutant ΔF508 of the cystic fibrosis transmembrane conductance regulator that is responsible for the onset of the severe disease cystic fibrosis in almost 70% of the cases (7). However, this mutant is exclusively localized in the ER and is therefore not implicated in a hypothetical quality control mechanism beyond the ER as proposed for SI phenotype II and the temperature-sensitive G protein. The arrest of the phenotype II of SI in the cis-Golgi coincides with a mutation of glutamine to proline at residue 1098 of the sucrase subunit (SIQ/P) (8). It is proposed that this mutation is harbored within a cryptic signal responsible for the retention of the mutant protein in the cis-Golgi. Presumably this mutation could have induced a limited structural alteration in the SI protein not monitored by the quality control machinery in the ER permitting the mutant protein to escape the ER up to the...
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**Materials and Reagents**—Streptomycin, penicillin, glutamine, Dulbecco’s modified Eagle’s medium, methionine-free Dulbecco’s modified Eagle’s medium, fetal calf serum, and trypsin were purchased from BioWest, Essen, Germany. Papsttin, leupeptin, aprotinin, trypsin inhibitor, and molecular mass standards for SDS-PAGE were purchased from Sigma. Soybean trypsin inhibitor was obtained from Roche Molecular Biochemicals.

**EXPERIMENTAL PROCEDURES**

**Construction of cDNA Clones**—The plasmid pSI-YFP-Q/P was generated with the QuikChange™ in vitro mutagenesis system from Stratagene according to the manufacturer’s instructions. The template pSI-YFP constitutes a full-length cDNA encoding pro-SI fused to the YFP gene according to the manufacturer’s instructions. The template pSI-YFP was isolated from the surface of COS-1 cells as described previously (14). The immunoprecipitates from transiently transfected, [35S]methionine-labeled COS-1 cells were treated with 2, 20, or 500 μg/ml trypsin inhibitor for 30 min at 37 °C. The reaction was terminated by cooling on ice at 4 °C and addition of 200 μg of soybean trypsin inhibitor (Roche Molecular Biochemicals).

**Transient Transfection of COS-1 Cells**—COS-1 cells were transiently transfected with pSG8-hSI or pSG8-SIQ/P. A 48 h after transfection the cells were pulsed with [35S]methionine for 1 h at 37 °C followed by different chase periods at 37 °C or 20 °C. After cell lysis pro-SI was immunoprecipitated with mAb anti-SI prior to SDS-PAGE. B, the transiently transfected COS-1 cells were biosynthetically labeled at 37 °C for 6 h or at 20 °C for 24 h followed by cell lysis and immunoprecipitation of SI. The immunoprecipitates were treated with varying concentrations of trypsin and processed by SDS-PAGE. The gels were analyzed by phosphorimaging.

**RESULTS AND DISCUSSION**

SI in phenotype II of CSID is predominantly expressed as an endoglycosidase H-sensitive mannose-rich polypeptide. Initial localization of SI in intestinal epithelial by immunoelectron microscopy using monoclonal anti-SI revealed an intensive labeling of the ER, the intermediate compartment ERGIC, and the cis-Golgi cisternae. Similar structural features and subcellular localization could also be demonstrated in non-intestinal cells as assessed in transfection experiments of mutant SI DNA in COS-1 cells. These observations clearly indicate that the function of the mutation Q1098P in the sucrose domain is not specific for intestinal or polarized cells. The partial intracellular localization of the SI phenotype II in the ER, ERGIC, and cis-Golgi suggests that minimal folding requirements of the mutant SI protein were fulfilled permitting a partially folded protein to egress the ER to the cis-Golgi. Fig. IA shows a pulse-chase analysis of COS cells expressing the mutant SIQ/P or wild type SI as a control. At physiological temperatures
of 37 °C, no conversion of the endoglycosidase H-sensitive mannosereich SIQ/P species to a complex glycosylated form could be observed as was seen in the control experiment. This indicates that the majority of the protein remains in the ER or is blocked in the cis-Golgi as previously demonstrated in immunofluorescence and electron microscopical analyses (8) (see also Fig. 2).

The arrest of the SIQ/P in the cis-Golgi is probably regulated by a quality control mechanism operating beyond the ER. It is likely that the proportion that makes it through the Golgi apparatus has probably acquired correct folding through several cycles of anterograde and retrograde transport between the cis-Golgi and the ER. We wanted therefore to determine whether slowing down the processing rate of the mutant SI protein and prolongation of its residence time in the ER influences its structural features and biological activity. Furthermore the pulse-chase experiments showed that the SIQ/P protein undergoes intracellular degradation at 37 °C. We therefore compared the fate of SIQ/P under the two different labeling temperatures, 20 °C and 37 °C. Here a dramatic difference in the turnover rates was observed. While SI was gradually degraded with increasing chase periods at 37 °C in Fig. 1A, longer chase periods of up to 24 h at 20 °C resulted in an efficient conversion of mannosereich SI, to a predominantly labeled complex glycosylated SI. Interestingly this protein was now as enzymatically active as its wild type SI counterpart (Ref. 18 and Table I).

To further examine the stability and folding of SIQ/P at the permissive temperature, we probed its sensitivity toward trypsin. Correctly folded wild type brush border SIc is processed in the intestinal lumen to the two subunits sucrase and isomaltase by pancreatic trypsin. Thereafter the two species remain associated with each other through strong non-ionic interactions and are trypsin-resistant (19, 20). Changes in the protein folding of SI would be therefore monitored by variation in its susceptibility to trypsin. As shown before (8, 9) and as indicated in Fig. 1B, trypsin resulted in a drastic degradation of SIQ/P.

**Table I**  
Enzymatic activity of SI in transfected COS-1 cells

| Temperature | SIw | SIQ/P |
|-------------|-----|-------|
| 20 °C       | 2.8 ± 0.4 | 2.6 ± 0.4 |
| 37 °C       | 3.1 ± 0.2 | 0.3 ± 0.05 |

**Fig. 2.** SIQ/P reaches the cell surface at permissive temperatures. A, monitoring of the SIQ/P passage from ER to Golgi at permissive temperatures. COS-1 cells were co-transfected with pSG8-hSI (B) or pSIQ/P-YFP (A, C, and D) and GT-CFP as Golgi marker. 24 h after transfection the cells were further incubated at 37 °C (A and B) or shifted to 20 °C (C and D). Confocal analysis of the cells was performed 48 h after transfection. In D the cells were incubated for 30 min at 37 °C to release proteins from the Golgi. In the merged pictures red indicates SI-YFP or SIQ/P-YFP labeling, and GT-CFP staining is depicted in green. Scale bars, 10 μm. E, isolation of SI and SIQ/P from the cell surface. COS-1 cells were transfected with pSG8-hSI or pSGSIQ/P. 48 h after transfection the cells were biosynthetically labeled at 37 °C for 12 h. Wild type or mutant SI was bound at the cell surface by mAb anti-SI at 4 °C. The cells were solubilized in lysis buffer, and the antigen-antibody complex was captured by protein A-Sepharose. The immunoprecipitates were processed by SDS-PAGE. The gels were analyzed by phosphorimaging. wt, wild type.
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By contrast, SI Q/P synthesized and processed at 20°C and Golgi as well as at the cell surface (Fig. 2). The wild type protein was detected in the data in which a predominant mannose-rich glycosylated protein was isolated from the cell surface indicating that this protein has reached the cell surface and thus confirming the fluorescence data. At 20°C no molecules were isolated from the cell surface, and the entire protein was retained intracellularly as it would be expected at this temperature. In sum, the data unequivocally demonstrate that the SI Q/P mutant is a typical temperature-sensitive mutant that acquires a complex glycosylated mature form at the permissive temperature and can be further transported thereafter to the cell surface at the non-permissive temperature. Notably this behavior indicates that the Q1098P mutation in the S subunit does not give rise to a Golgi retention signal but rather generates a folding determinant that cannot overcome a potential quality control operating in the cis-Golgi where phenotype II of CSID is blocked (21).

The temperature-sensitive properties of SI Q/P prompted us to investigate the interaction of this mutant with proteins of the folding machinery, such as BiP and calnexin, and compare this interaction to that of the wild type counterpart. First we analyzed the steady state binding of these proteins to the SI forms. Here transfected COS-1 cells expressing wild type as well as mutant SI were biosynthetically labeled with [35S]methionine continuously for 6 h, and the cellular detergent extracts were immunoprecipitated with anti-BiP or anti-calnexin antibodies. The antigenic material bound to the beads was eluted and examined for the presence of SI by immunoprecipitation with mAb anti-SI. As shown in Fig. 3A the binding of BiP to the wild type protein occurs during early stages of the biosynthesis when the SI protein is in its mannose-rich glycosylated form. This is in line with the pattern established for a variety of proteins interacting with this molecular chaperone. Likewise BiP was found associated with the mannose-rich form of the mutant SI Q/P form. This mutant, however, bound more strongly than the wild type protein supporting a prolonged intracellular localization of this form in the ER. Similar binding profiles were obtained with calnexin (Fig. 3A). Here again calnexin bound more strongly the SI Q/P mutant than the wild type species. The binding kinetics of BiP and calnexin to the wild type and mutant forms SI were assessed by using a pulse-chase protocol. As shown in Fig. 3B BiP and calnexin bound strongly to the mannose-rich mutant SI Q/P during the first time interval after 30 min of pulse. The binding capacity to BiP diminished after 30 min of chase at 20°C, whereas the amount of mannose-rich mutant SI Q/P bound to calnexin was increased at this time point. These patterns changed after 60 min of chase with a significant binding of SI Q/P to BiP and to a lesser extent to calnexin. Essentially a reversed binding pattern was obtained within 240 min of chase. Here more SI Q/P molecules were found associated with calnexin than with BiP, indicating that the mutant SI polypeptide is subject to cycles of association, disso-

Fig. 3. Sequential interaction of SI Q/P with BiP and calnexin. COS-1 cells were transfected with pSG8-hSI and pSG8-SI Q/P. A, 48 h post-transfection the cells were biosynthetically labeled at 37°C for 6 h followed by cell lysis and immunoprecipitation of SI. The cell lysates were immunoprecipitated with anti-BiP or anti-calnexin and subsequently with mAb anti-SI. B, transiently transfected COS-1 cells were labeled for 30 min followed by different chase intervals at 20°C. The cell lysates were immunoprecipitated sequentially with mAb anti-SI and anti-BiP or anti-calnexin. The samples were analyzed by SDS-PAGE and phosphorimaging. IP, immunoprecipitation.

SI Q/P synthesized at 37°C, the non-permissive temperature. By contrast, SI Q/P synthesized and processed at 20°C was digested to a pattern similar to the wild type protein, i.e., to the individual subunits I and S (Fig. 1B) (note that the almost similar apparent molecular weights of I and S as well as their heavy glycosylation do not allow a clear separation of the two subunits electrophoretically (20)). Further digestion with trypsin did not generate any alteration in the electrophoretic pattern compatible with a trypsin-resistant profile of SI Q/P synthesized and processed at 20°C.

The acquisition of a complex glycosylated protein pattern as well as trypsin resistance at 20°C similar to the wild type enzyme indicates that SI Q/P exhibits characteristics of a temperature-sensitive protein. Under these conditions the SI Q/P protein exits the ER and is processed in the Golgi apparatus more efficiently than is the protein synthesized at 37°C. We assessed therefore the intracellular localization of the SI Q/P at the various temperatures and determined whether this form is capable of reaching the cell surface after the temperature block has been eliminated. For this, the trafficking of SI Q/P as compared with the wild type species was examined in transfected COS-1 cells using confocal laser microscopy at the permissive and non-permissive temperatures. The cDNA encoding SI Q/P fused to the yellow variant of the green fluorescent protein (pSI Q/P-YFP) was used. Confocal analysis of these cells at 37°C revealed a predominant uniform pattern of distribution of SI Q/P-YFP in the ER (Fig. 2A) and to some extent in the Golgi area. This is in line with the biochemical data in which a predominant mannose-rich glycosylated protein was detected. The wild type protein was detected in the ER and Golgi as well as at the cell surface (Fig. 2B). At 20°C the SI Q/P protein was predominantly localized to the Golgi membranes as assessed by the strong labeling of this organelle in cells expressing the SI Q/P-YFP protein (Fig. 2C). This result supports the biochemical analysis, which demonstrated a substantial conversion of the mannose-rich species to the complex glycosylated mature protein. We next asked whether the acquired complex glycosylation of the SI Q/P mutant protein in the Golgi apparatus at 20°C was sufficient for its further trafficking to the cell surface or whether the Q1098P mutation per se does hamper this transport despite maturation and retains the protein in the Golgi. Many membrane and secretory proteins that are destined for the cell surface undergo a transport block in the Golgi apparatus at 20°C. This block is eliminated, and the protein transport continues at the physiologic temperature of 37°C. To determine whether the SI Q/P mutant processed at 20°C is capable of exiting the Golgi, the cells expressing the SI Q/P mutant were incubated at 37°C for 30 min after the 20°C block (Fig. 2D). Confocal images in living transfected cells show that SI Q/P-containing vesicles have started to pinch off the trans-Golgi network membrane, and some vesicles have already exited this organelle. These vesicles were devoid of the Golgi protein marker galactosyltransferase (GT). To corroborate these data by a different approach cell surface immunoprecipitation of biosynthetically labeled cells expressing the SI Q/P mutant was performed (Fig. 2E). Here the cells were labeled at 20°C followed by a chase at 37°C. The complex glycosylated SI Q/P molecule was isolated from the cell surface indicating that this protein has reached the cell surface and thus confirming the fluorescence data. At 20°C no molecules were isolated from the cell surface, and the entire protein was retained intracellularly as it would be expected at this temperature. In sum, the data unequivocally demonstrate that the SI Q/P mutant is a typical temperature-sensitive mutant that acquires a complex glycosylated mature form at the permissive temperature and can be further transported thereafter to the cell surface at the non-permissive temperature. Notably this behavior indicates that the Q1098P mutation in the S subunit does not give rise to a Golgi retention signal but rather generates a folding determinant that cannot overcome a potential quality control operating in the cis-Golgi where phenotype II of CSID is blocked (21).

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ciation, and reassociation with the ER-resident proteins BiP and calnexin. The sequential pattern of association of SI_{Q/P} with BiP and calnexin changes when the protein is adequately folded to be transported to the medial and trans-Golgi where it matures to a complex glycosylated protein at the permissive temperature.

In conclusion, the mutant SI_{Q/P} reveals characteristics of a temperature-sensitive mutant. Temperature-sensitive mutants of a gene are characterized by a marked drop in the level of activity or altered structural features of the gene product when the gene is expressed above a certain temperature (the non-permissive temperature). Below this temperature the activity and structure are recovered and are usually very similar to that of wild type. The acquisition of correct folding at the cis-Golgi is in all likelihood the result of an anterograde and retrograde transport between the ER and the cis-Golgi. This is supported by the observation that several cycles of association and dissociation with the molecular chaperones BiP and calnexin take place. In this mechanism calnexin plays a central role as a C-terminally located intramolecular chaperone in the folding of isomaltase by competing with calnexin in the binding to similar sites in isomaltase (22). The mutation Q1098P, which is located in the intramolecular chaperone sucrase, generates a misfolded sucrase species as shown by epitope mapping with monoclonal antibodies (9) with a subsequent loss of its function as an efficient competitor for calnexin in binding the isomaltase subunit. At the permissive temperature sucrase becomes correctly folded and capable of competing again with calnexin, substituting for calnexin, and generating a correctly folded pseudodimer with isomaltase.

The mechanism proposed here is to our knowledge not only the first of its kind reported for an intestinal enzyme deficiency or an intestinal disorder but also for an endogenous cell surface membrane protein. Another known case of a protein that recycles between the ER and the Golgi is that of the tsO45 mutant of the G protein of the vesicular stomatitis virus (6). However, overexpression of the viral protein and possible saturation of the quality control machinery in the ER are factors that do not conform to the in vivo situation of an endogenous protein such as SI.

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