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The ER Glycoprotein Quality Control System

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Abstract

The endoplasmic reticulum (ER) is the major site for folding and sorting of newly synthesized secretory cargo proteins. One central regulator of this process is the quality control machinery, which retains and ultimately disposes of misfolded secretory proteins before they can exit the ER. The ER quality control process is highly effective and mutations in cargo molecules are linked to a variety of diseases. In mammalian cells, a large number of secretory proteins, whether membrane bound or soluble, are asparagine (N)-glycosylated. Recent attention has focused on a sugar transferase, UDP-Glucose: glycoprotein glucosyl transferase (UGGT), which is now recognized as a constituent of the ER quality control machinery. UGGT is capable of sensing the folding state of glycoproteins and attaches a single glucose residue to the $Man_9GlcNAc_2$ glycan of incompletely folded or misfolded glycoproteins. This enables misfolded glycoproteins to rebind calnexin and reenter productive folding cycles. Prolonging the time of glucose addition on misfolded glycoproteins ultimately results in either the proper folding of the glycoprotein or its presentation to an ER associated degradation machinery.

Introduction

UDP-Glucose: glycoprotein glucosyl transferase (UGGT) is a lumenal endoplasmic reticulum (ER) enzyme that plays a sensor role in a molecular machine known as the calnexin/calreticulin (CNX/CRT) cycle (Figure 1) (for recent reviews, Helenius *et al*., 1997; Zapun *et al*., 1999; Jakob *et al*., 2001b; Parodi, 2000). The principal constituents of this molecular machine are two lectins, the ER transmembrane protein calnexin (Bergeron *et al*., 1994) and its soluble lumenal paralogue calreticulin (Michalak *et al*., 1999), and the enzymes glucosidase II (Brada and Dubach, 1984; Trombetta *et al*., 1996) and UGGT (Sousa *et al*., 1992; Trombetta and Parodi, 1992). In the ER lumen, the asparagine (N)-linked oligosaccharides of newly synthesized glycoproteins undergo trimming by glucosidases (Brada and Dubach, 1984; Hettkamp *et al*., 1984; Trombetta *et al*., 1996) immediately after transfer of the core glycan, $Glc_3Man_9GlcNAc_2$, to the asparagine residue within the consensus sequence Asn-X-Ser/Thr (where X is any amino acid except proline) of the growing polypeptide chain (Kornfeld and Kornfeld, 1985; Burda and Aebi, 1999). Membrane bound glucosidase I (Hettkamp *et al*., 1984) and the soluble glucosidase II (Brada and Dubach, 1984; Trombetta *et al*., 1996) remove the alpha 1,2-glucose and alpha 1,3-glucose residues, respectively. The sequential action of glucosidase I and II generates glycoproteins having the monoglucosylated oligosaccharide $Glc_1Man_9GlcNAc_2$, which is a substrate for binding to CNX/CRT (Hammond *et al*., 1994). Calnexin and calreticulin also interact with the PDI orthologue ERp57. This interaction assists in disulfide interchange of calnexin associated glycoproteins (Oliver *et al*., 1997; Zapun *et al*., 1998; Molinari and Helenius, 1999). Glucosidase II, apparently irrespective of the protein conformation, trims the last glucose residue on the oligosaccharide side chain of glycoproteins (Pelletier *et al*., 2000; Schrag *et al*., 2001; Zapun *et al*., 1997; Rodan, 1996), thus eliminating their recognition by calnexin or calreticulin. Conversely, UGGT can add back a single glucose unit from UDP-Glc in an α(1-3) bond to the terminal mannose of the α(1-3)-α(1-2) branch of $Man_{7\text{-}9}GlcNAc_2$, restoring the monoglucosylated oligosaccharide molecule as a substrate for CNX/CRT interaction (Parodi, 2000; Rodan *et al*., 1996; Sousa and Parodi, 1995; Trombetta and Parodi, 1992; Wada *et al*., 1997; Zapun *et al*., 1997). The sum of the action of the three components is to act as a molecular chaperone to detain incompletely folded proteins in the ER. That UGGT was a component of such a molecular chaperone system became apparent following the discovery by Parodi that the enzyme targets denatured substrates which may be taken as surrogates for incorrectly folded proteins (Parodi, 2000). UGGT can sense and select incompletely folded glycoproteins for a further cycle of folding (Parodi, 2000; Zapun *et al*., 1997; Rodan *et al*., 1996; Sousa and Parodi, 1995; Wada *et al*., 1997), as well as discriminate among different nonnative conformers (Parodi, 2000; Sousa *et al*., 1992; Rodan *et al*., 1996; Sousa and Parodi, 1995). If the protein is folded, it is not reglucosylated and escapes this cycle, thereby releasing the glycoprotein to exit from the ER, after ER mannosidase processing. If secretory proteins fail to fold correctly in the ER, they are targeted to the ER-associated degradation (ERAD) machinery (Fewell *et al*., 2001; Hampton, 2002; Jarosch *et al*., 2002), also after ER mannosidase processing (Weng and Spiro, 1993; Jelinek-Kelly and Herscovics, 1988) and the downstream involvement of a novel lectin (Mn11p/ Htm1p / EDEM; Hosokawa *et al*., 2001; Jakob *et al*., 2001a; Nakatsukasa *et al*., 2001; Figure 1). Collectively, these mechanisms have been referred to as the ER quality control of protein folding and degradation (for recent reviews, Helenius *et al*., 1997; Jakob *et al*., 2001a; Parodi, 2000; Zapun *et al*., 1999). UGGT is the sole known constituent of the calnexin cycle to read the polypeptide code for folding and thereby distinguish

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between productively folded and misfolded glycoproteins (Zapun *et al.*, 1999). However, the molecular mechanisms by which this process happens remain unclear. The identification of UGGT isoforms without glucosyl transferase activity further adds to the complexity of the sensors of glycoprotein folding. Understanding the mechanism of glycoprotein recognition of by the UGGT family may be of relevance to protein trafficking diseases.

UDP-Glucose:glycoprotein glucosyl transferase

The enzyme activities have been partially characterized from Trypanosoma cruzi (Parodi and Cazzulo, 1982; Parodi, 2000), *Schizosaccharomyces pombe* (Fernandez *et al.*, 1994), *Drosophila melanogaster* (Parker *et al.*, 1995) and rat liver (Trombetta and Parodi, 1992). UGGT is ubiquitously expressed in the ER of most eukaryotic species (Trombetta *et al.*, 1989) and has been sequenced from different sources (Arnold *et al.*, 2000; Fernandez *et al.*, 1994; Parker *et al.*, 1995; Tessier *et al.*, 2000). Recombinant rat (Tessier *et al.*, 2000) and human (Arnold *et al.*, 2000) UGGTs have been expressed in insect and mammalian cells, respectively. The rat enzyme is a large, soluble glycoprotein of 170 kD with an ER localization signal (variants of the His-Asp-Glu-Leu (HDEL) retention signal) at its C-terminus. It is present in the ER lumen (Parodi, 2000; Trombetta and Parodi, 1992) and in pre-Golgi intermediates (Zuber *et al.*, 2001). The optimal enzyme activity is at neutral pH and is Ca^{2+} or Mn^{2+}-dependent (for a recent review, Parodi, 2000).

Classification of known glycosyltransferases has been based on sequence homologies (Breton *et al.*, 1998; Campbell *et al.*, 1997). Recently, the *D. melanogaster* and *S. pombe* UGGT homologues (which are grouped with *C. elegans* 2, and the sequence related killer toxin-resistance protein Kre5p from *S. cerevisiae* (Meaden *et al.*, 1990) into family 24 in ref. Campbell *et al.*, 1997) were placed in the galactosyltransferase Family B by their structural homology to bacterial proteins (the glycosyltransferases of family 8 in ref. Campbell *et al.*, 1997) involved in lipopolysaccharide core biosynthesis (Breton *et al.*, 1998). The full-length sequence alignments of known and putative UGGTs reveals a highly conserved 300 amino acid sequence (30% of the molecule, 60-70% identity) in the C-terminal domain (Breton *et al.*, 1998; Tessier *et al.*, 2000) (Figure 2). Limited but significant similarity exists between this highly conserved domain and several bacterial transferases that utilize UDP-Glc or UDP-Gal as a substrate donor (Breton *et al.*, 1998). Therefore, the C-terminal domain of UGGT is responsible for recognition of the donor nucleotide-sugar and likely contains the catalytic domain: In this C-terminal region, two conserved motifs have been detected. DxD (x is any amino acid) is the most conserved motif observed in the galactosyltransferase Family B (Figure 2) which probably provides the binding site for the UDP-sugar (Tessier *et al.*, 2000; Arnold *et al.*, 2000) and DQDxxN which is probably involved in recognition of the N-acetylglucosamine residue linked to the Asn residue of the glycoprotein substrate to which the sugar is transferred (Tessier *et al.*, 2000; Arnold *et al.*, 2000). The N-terminal domains of UGGTs reveal a lower degree of sequence similarity and have been proposed to be responsible for the recognition of protein conformations (Parodi, 2000; Guerin and Parodi, 2003).

Substrate recognition by UGGT

UGGT can recognize both the glycan and the protein moiety of incompletely folded glycoproteins, preferentially in molten globule-like conformers (Parodi, 2000; Caramelo *et al.*, 2003; Sousa *et al.*, 1992; Sousa and Parodi, 1995). The innermost GlcNAc unit of the glycoprotein's oligosaccharide is proposed to be required for UGGT recognition. Denatured nonglucosylated proteins do not affect UGGT activity, whereas denatured glycoproteins from which oligosaccharides have been removed by endo-β-N-acetylglucosaminidase H (Endo H) treatment (*i.e.* leaving a single GlcNAc-Asn) are efficient inhibitors of UGGT activity (Sousa and Parodi, 1995), but Endo H digested native glycoproteins with a remaining GlcNAc residue are not inhibitors of UGGT activity (Parodi, 2000; Sousa and Parodi, 1995). Thus, this innermost GlcNAc moiety must be covalently linked to a denatured glycoprotein. UGGT then recognize the covalently-linked $Man_9GlcNAc_2$ denatured protein as substrate (Sousa and Parodi, 1995).

The exposed hydrophobic patches in incompletely folded glycoproteins, that would otherwise be hidden domains in native conformers, are recognized by the enzyme (Sousa *et al.*, 1992; Sousa and Parodi, 1995). This is supported by observations demonstrating that interaction with immobilized hydrophobic stretches, but not with hydrophilic peptides, is inhibited by denatured but not by native glycoproteins (Sousa *et al.*, 1992; Sousa and Parodi, 1995). Consequently, it has been proposed that UGGT senses the exposed hydrophobic residues in a way similar to many classical molecular chaperones (Sousa and Parodi, 1995).

To date, it has been unclear how these exposed hydrophobic stretches influence UGGT's ability to recognize and reglucosylate its substrates. However, hydrophobic residues on substrate glycoproteins may directly and/or with other molecular chaperones (BiP [binding protein, a member of the heat shock protein 70 family]) enhance the preferential selectivity of UGGT for incompletely folded glycoproteins (Caramelo *et al.*, 2003; Taylor *et al.*, 2003). In contrast to previous reports, it has recently been shown that short glycopeptides with different amino acid sequences are recognized by UGGT. Furthermore, hydrophobic residues close to N-linked glycan seem to be the main determinant for recognition by UGGT (Taylor *et al.*, 2003). We speculate that these peptide-recognition elements may be in close proximity to glycans in folding intermediates (Taylor *et al.*, 2003). Although both proteins recognize hydrophobic patches exposed during folding process, UGGT glucosylates glycoproteins preferentially in molten globule-like conformations, whereas BiP recognizes heptapeptides with large hydrophobic residues (Blond-Elguindi *et al.*, 1993) in an extended structure (Caramelo *et al.*, 2003). It has consequently been speculated that BiP would interact with a relatively extended structure in early stage of glycoprotein folding rather than UGGT. This is consistent with other observations that

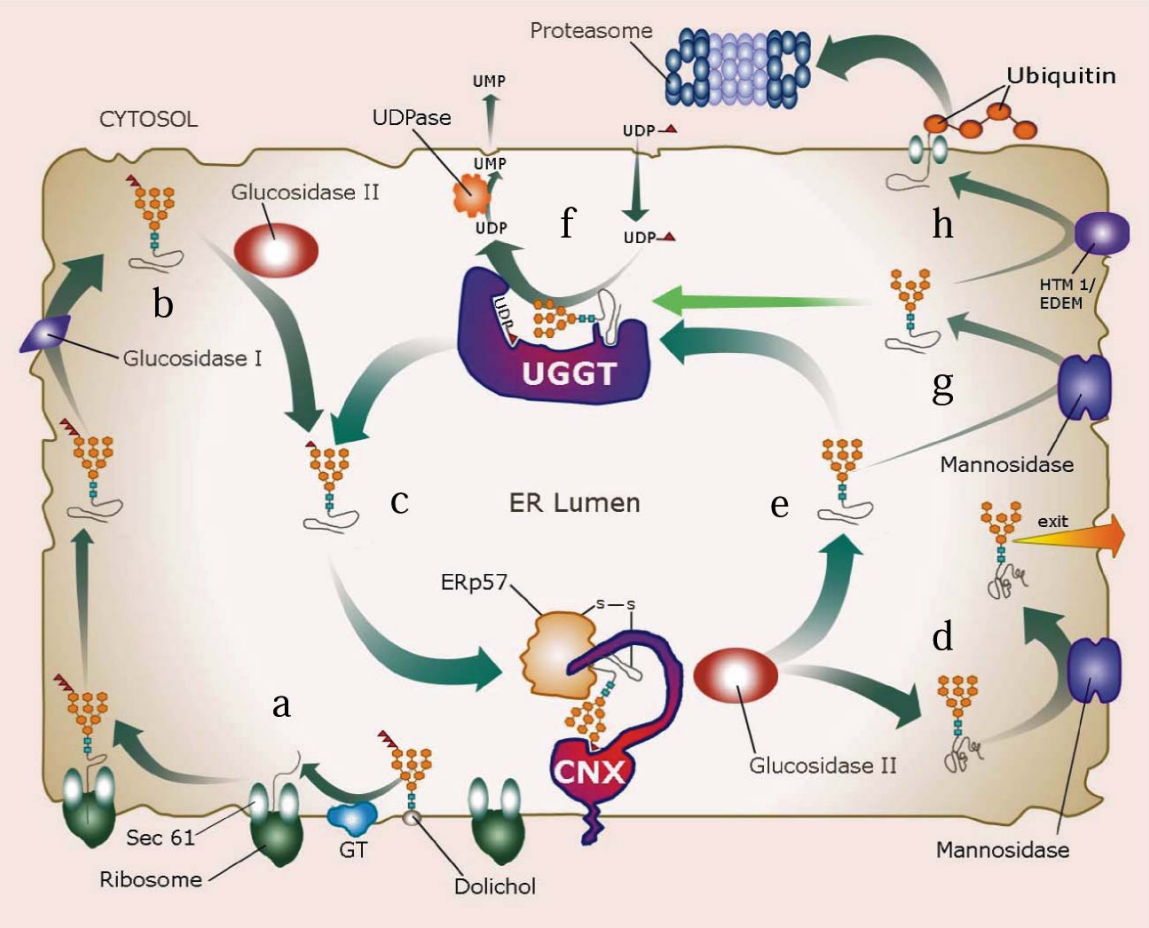

Figure 1. CNX/CRT cycle. In the ER, the action of two enzymes, glucosidase II and UGGT, regulate the release and binding of glycoproteins to CNX/CRT providing a unique quality control mechanism known as the CNX/CRT cycle (Helenius *et al.*, 1997) for glycoprotein folding. (a) The precursor glycan ($Glc_3Man_{5\text{-}9}GlcNAc_2$) linked to the lipid molecule, dolichol (Burda and Aebi, 1999), is transferred to the NH2 group on the side chain of asparagine residues positioned in a consensus sequence Asn-X-Ser/Thr (where X is any amino acid except proline) in the growing, nascent polypeptide chain (Kornfeld and Kornfeld, 1985), as soon as it enters the ER lumen via the Sec61p translocon complex (Lodish *et al.*, 1983). The transfer is catalyzed by membrane-bound glycosyl transferases, which recognizes a specific conformation of Asn-X-Ser/Thr sequences (Silberstein and Gilmore, 1996). (b) Glucosidase I and II successively trim two of the glucose residues leaving the $Glc_1Man_9GlcNAc_2$ core oligosaccharide. (c) Calnexin and its lumenal paralogue calreticulin are lectins that specifically bind monoglucosylated oligosaccharides, and present them to the glycoprotein-specific thiol oxidoreductase, ERp57, which also bound to CNX/CRT. If the complete deglucosylation of glycoproteins occurs before the CNX-glycoprotein interaction, the monoglucosylated glycoproteins are also generated by reglucosylation through the action of UGGT. Trimming of the last glucose residue by glucosidase II terminates the calnexin-glycoprotein interaction. If the proteins are correctly folded (d) they proceed further into the secretory pathway, whereas incompletely folded proteins (e) are recognized by UGGT. (f) UGGT reglucosylates incompletely folded proteins by readdition of a single glucose residue from UDP-Glc thereby generating a substrate for the calnexin cycle. UDP-Glc is transported into the ER lumen from the cytosol and is exchanged to uridine monophoshate (UMP) by uridine diphosphatase (UDPase) (Trombetta and Helenius, 1999), and UMP is transported back to cytosol. (g) The CNX/CRT cycle continues until the proteins are correctly folded or directed to ER-associated degradation (ERAD) after trimming by ER α1,2-mannosidases. (h) An enzymatically inactive member of this protein family, ER Degradation Enhancing α-Mannosidase-like protein (EDEM) and the yeast homologue Mn11p (mannosidase-like protein) or Htm 1p (homologous to mannosidase I, shown as HTM 1) may participate as lectins and promote ERAD of incorrectly folded proteins that are then transported to the cytosol via the Sec61p translocon complex where they are proteolytically degraded by the proteasome system, in most cases following polyubiquitination.

UGGT functions at later stages of glycoprotein folding (Parodi, 2000) and efficiently recognizes a variety of partially folded conformers (Trombetta and Helenius, 2000). Indeed, it has been shown that UGGT glucosylates the endogenous trypanosome substrate of UGGT, cruzipain (a lysosomal cysteine proteinase with two or three N-linked oligosaccharides and six or seven disulfide bridges) after it has obtained a tertiary structure that closely resembles the native conformer (Parodi, 2000). Since hydrophobic patches on glycoprotein substrates are introduced into a cleft in the bacterial homolog of BiP (DNaK) structure, it is then suggested that UGGT might require a larger surface interaction with its substrate glycoproteins for reglucosylation than BiP (Caramelo *et al.*, 2003).

In addition, in glycoproteins with multiple independently folding domains, UGGT recognizes folding defects at the level of individual domains and only reglucosylates glycans in the misfolded domains (Ritter and Helenius, 2000). This may allow the CNX/CRT cycle to interact with only unfolded parts of the glycoproteins depending on distribution of

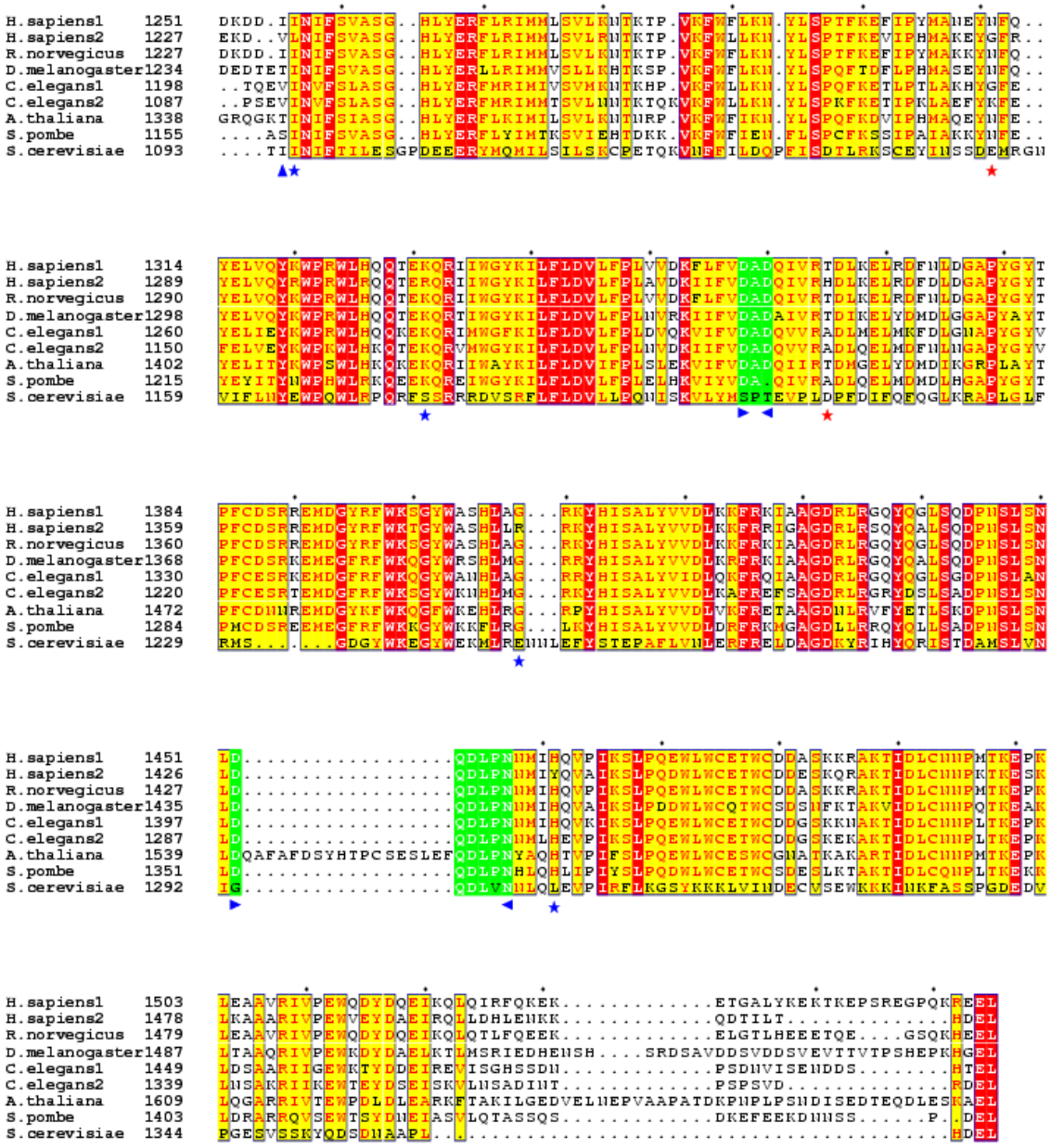

Figure 2. Alignment of protein sequences from UGGTs in the C-terminal region of the protein. Although the cDNA sequence encoding UGGT protein from different sources shows a high degree of sequence homology extending over the entire sequence of the protein, it is particularly high in the C-terminal region of the protein. The color key is: red box, white letter for strict identity, red character for similarity in a group, blue frame filled in yellow shows similarity across groups. The boundary of the proposed catalytic domain (is shown with ▲) identified for *H. sapiens1* (Arnold *et al.*, 2000) is about 300 residues from the C-terminus. Highly conserved catalytic domain motifs (in *H. sapiens* UGGT 1 sequence, residues 1357-1360 and 1452-1457 respectively) in all UGGTs except *S. cerevisiae* Kre5p are shown with ◗ ◖, in green box, white letter. Conserved residues in all homologues but both *H. sapiens* UGGT 2 (Arnold *et al.*, 2000) and *S. cerevisiae* (except the first residue) are denoted with blue ★ under the sequences (in hUGGT1 sequence, I 1256, K 1331, G 1409, H 1461). Other candidate residues that differ from the known active UGGTs (*H. sapiens*1, *R. norvegicus*, *D. melanogaster*, *S. pombe* UGGT proteins) for the inactive UGGT sequences (*H. sapiens*2 and *S. cerevisiae* proteins) are donated with red ★ under the sequences (in hUGGT1 sequence, N 1311, T 1365).

glycosylation sites. Such recognition may be important for large molecules that have multiple independently folding domains (Ritter and Helenius, 2000). This then raises the more fundamental question that concerns the evolution of N-linked sites of glycosylation in mammalian glycoproteins. Have these sites evolved to identify locations in a polypeptide that are critical to UGGT-mediated presentation to the CNX/CRT cycle? The degree of conservation of most N-linked glycans in glycoproteins is high (Dwek *et al.*, 2002; Rudd *et al.*, 2001a; Rudd *et al.*, 2001b; Rudd *et al.*, 2001c). For viral envelope glycoproteins, all of which use the CNX/CRT cycle for productive folding, these conserved sites of N-linked glycosylation have evolved as essential for viral biogenesis (Rudd *et al.*, 2001a; Rudd *et al.*, 2001b; Rudd

et al., 2001c). Hence, evolution may have selected the polypeptide domains within which a subset of N-glycans is found for presentation to UGGT as part of the protein folding code required for correct glycoprotein folding in the calnexin cycle.

UGGT in quality control, degradation and sorting

Quality control

Calnexin and/or calreticulin bind transiently to almost all soluble and membrane bound glycoproteins during folding or oligomeric assembly of the glycoproteins in the ER (Hammond *et al*., 1994; Helenius *et al*., 1997; Ou *et al*., 1993). Trypanosomatid protozoa cells express calreticulin but lack calnexin and in these cells $Man_{6\text{-}7}GlcNAc_2$, or $Man_9GlcNAc_2$ is transferred to the nascent polypeptide chain by oligosaccharyltransferase. Thus, in these cells creation of a $Glc_1Man_9GlcNAc_2$ glycoprotein that can bind calreticulin is only via the action of UGGT (Labriola *et al*., 1999; Parodi and Cazzulo, 1982). In contrast, all mammalian species transfer triglucosylated (*i.e.* $Glc_3Man_9GlcNAc_2$) structures to nascent polypeptide chains and also possess UGGT and thus there is a dual route of presentation to CNX/CRT either via the sequential activity of glucosidase I and II or by reglucosylation by UGGT (Parodi, 2000). This difference between cells from various trypanosome species and mammalian cells may predict regulation of entry into the CNX/CRT cycle at the level of substrates presented to the oligosaccharyltransferase. Such a regulation of dolichol-based intermediates in the biosynthetic pathway of $Glc_3Man_9GlcNAc_2$ has recently been observed in normal primary cells undergoing a stress response (Doerrler and Lehrman, 1999), although its precise physiological significance remains to be established. Misfolded glycoproteins enter a cycle of binding to and release from CNX/CRT mediated by the sequential actions of UGGT and glucosidase II as originally proposed by Hammond *et al* (Hammond *et al*., 1994; Parodi, 2000; Trombetta and Parodi, 1992). This ultimately results in either the proper folding of the glycoprotein or its disposal (Fewell *et al*., 2001; Helenius *et al*., 1997; Jarosch *et al*., 2002; Ou *et al*., 1993; Parodi, 2000). In this context, the CNX/CRT cycle acts as a kinetic trap, retaining conformers that are not correctly folded, and allowing only the native conformers to move further along the secretory pathway (Labriola *et al*., 1999; Le *et al*., 1994; Ou *et al*., 1993; Pind *et al*., 1994). In support of this suggestion is the observation that the ER retention half-times of glycoproteins correlate with half times of their secretion, as well as their rank order of calnexin binding (Lodish *et al*., 1983; Ou *et al*., 1993). The demonstration in mammalian cells that UGGT activity can transform intermolecular oxidized aggregates of misfolded transferrin, a secretory glycoprotein of the liver, into monomeric productively folded transferrin is good evidence that reglucosylation by UGGT has a central role in quality control *in vivo* (Wada *et al*., 1997).

Most of the glycoproteins are reglucosylated during their maturation in the ER, including influenza HA (Hebert *et al*., 1995), vesicular stomatitis virus G protein (Suh *et al*., 1989), transferrin (Wada *et al*., 1997), T cell receptor subunits (Van Leeuwen and Kearse, 1997) and cruzipain (Labriola *et al*., 1999). Reglucosylation may mediate the selection of the chaperones *in vivo* (Trombetta and Helenius, 2000). For example, vesicular somatitis virus glycoprotein binds to BiP during its early stage of folding, and later it is possible that reglucosylation mediates its binding to calnexin (Hammond *et al*., 1994). Recently, it has been speculated (Caramelo *et al*., 2003) that the preferential recognition of the glycoprotein substrates by UGGT and BiP might provide a molecular rationale for sequential interaction between BiP and CNX/CRT with folding glycoproteins (Hammond *et al*., 1994; Kim and Arvan, 1995; Molinari and Helenius, 2000).

In vitro, both UGGT and glucosidase II showed the highest relative rate of glucosylation/deglucosylation for glycoproteins containing $Man_9GlcNAc_2$ (Grinna and Robbins, 1980; Sousa *et al*., 1992). Relative glucosylation rates by UGGT were respectively 100, 50, and 15 for Man_9, Man_8, and Man_7 (Parodi, 2000; Sousa and Parodi, 1995). Similar to UGGT, glucosidase II also revealed reduced deglucosylation rates for substrate glycoproteins upon the removal of mannose residues (Grinna and Robbins, 1980). Hence these data led to a proposal that quality control in the ER is also regulated by demannosylation (Cabral *et al*., 2001).

ER-associated degradation

ER-associated degradation has a central clearance function in the cell (Fewell *et al*., 2001; Hampton, 2002; Jarosch *et al*., 2002). In this pathway, terminally misfolded proteins are subjected to trimming by ER α1,2-mannosidase(s) (Jelinek-Kelly and Herscovics, 1988; Weng and Spiro, 1993) and are transported to the cytosol via the Sec61p translocon complex (Pilon *et al*., 1997; Wiertz *et al*., 1996). They are then polyubiquitinated and proteolytically degraded by the cytosolic 26S proteasome. Ubiquitination appears to be required for both retrotranslocation to the cytosol and proteasomal degradation (see in reviews, Fewell *et al*., 2001; Hampton, 2002; Jarosch *et al*., 2002).

The relatively slow-acting ER α1,2-mannosidase is responsible for mannose trimming of the oligosaccharide side chain, irrespective of the protein conformation, generating primarily $Man_8GlcNAc_2$ isomer B in mammalian cells (Weng and Spiro, 1993), and only $Man_8GlcNAC_2$ isomer B in *S. cerevisiae* (Jelinek-Kelly and Herscovics, 1988). The resulting Man_8 structure can be recognized by an enzymatically inactive mannosidase I, called Mn11p (mannosidase-like protein; Nakatsukasa *et al*., 2001) or Htm1p (homologous to mannosidase I; Jakob *et al*., 2001a) in yeast and EDEM (ER Degradation Enhancing α-Mannosidase-like protein; Hosokawa *et al*., 2001) in mammalian cells. EDEM seems to be up-regulated by the unfolded protein response through the XBP1 pathway (Yoshida *et al*., 2003) and to target the misfolded protein for retrotranslocation and degradation by promoting release from the calnexin (Molinari *et al*., 2003; Oda *et al*., 2003). Calnexin, BiP and PDI have also been proposed to work in the recognition phase of misfolded glycoproteins for subsequent retrotranslocation and degradation (Molinari *et al*., 2002). Other factors may participate in the targeting

Table 1. List of diseases and ER quality control implications*

Disease	Protein	Glycoprotein	CNX/CRT Assoc.
I: Loss of coupling to ER export leading to degradation			
Cystic fibrosis (Pind *et al*., 1994)	Cystic fibrosis transmembrane regulator	+	CNX, Prolonged Assoc.
Hereditary emphysema (Le *et al*., 1994; Spiro *et al*., 1996)	α1-Antitrypsin (non PiZ variants)	+	CNX, Prolonged Assoc.
Hereditary hemochromatosis (Kühn, 1999)	HFE. Loss of binding transferrin receptor	+	
Protein C deficiency (Tokunaga *et al*., 2000)	Protein C	+	CNX/CRT
Type 1 hereditary angioedema (Verpy *et al*., 1993)	Complement C1 inhibitor	+	CNX
Tay-Sachs (Kaback and Desnick, 2001)	β-Hexosaminidase	-	
Congenital sucrase-isomaltase deficiency (Naim *et al*., 1988)	Sucrase-isomaltase	+	
Crigler-Najjar type II (Sampietro and Iolascon, 1999)	Bilirubin-UDP-glucuronosyltransferase 1	+	
Polyendocrinopathy/Hyperinsulemia (Reznik and Fricker, 2001)	Carboxypeptidase E	+	
Diabetes mellitus (Bass *et al*., 1998)	Insulin receptor	+	CNX/CRT, Prolonged Assoc.
Laron syndrome (Amselem *et al*., 1991)	Growth hormone receptor	+	
Hereditary myleoperoxidase (Nauseef, 1999; Nauseef *et al*., 1998)	Myeloperoxidase	+	CNX/CRT, Prolonged Assoc.
Primary hypoparathyroidism (Garfield and Karaplis, 2001)	Preproparathyroid hormone	-	
Oculocutaneous albinism (Halaban *et al*., 1997; Halaban *et al*., 2002; Vinayagamoorthy and Rajakumar, 1996)	Tyrosinase	+	CNX, Prolonged Assoc.
Fabry disease (Ishii *et al*., 2000)	α-D-galactosidase	+	
Congenital long QT syndrome (Deutsch, 2002; Furutani *et al*., 1999)	Voltage gated potassium channel (HERG)	+	CNX transient assoc.
Autosomal dominant retinitis pigmentosa (Frederick *et al*., 2001; Saliba *et al*., 2002; Illing *et al*., 2002)	Rhodopsin	+	
Lipid processing deficiencies			
Familial hypercholesterolemia (Jorgensen *et al*., 2000)	Low-density lipoprotein receptor	-	
Type 1 chylomicronemia (Ben-Zeev *et al*., 2002)	Lipoprotein lipase	-	CNX
Abetalipoproteinemia (Kim and Arvan, 1998)	Microsomal triglyceride transfer protein	+	
Low plasma lipoprotein (a) levels (White *et al*., 1999; Bonen *et al*., 1998)	Apolipoprotein (a)	-	CNX, Prolonged Assoc.
II: Loss of coupling to ER export leading to accumulation in the ER			
Liver diseases/Hereditary emphysema (Qu *et al*., 1997; Coakley *et al*., 2001)	α1-Antitrypsin (PiZ variants)	+	CNX
Congenital hypothyroidism/related disorders (Kim and Arvan, 1998)			
Thyroglobulin deficiency (Kim and Arvan, 1995)	Thyroglobulin	+	CNX/CRT, Prolonged Assoc.
Thyroid peroxidase deficiency (de Carvalho *et al*., 1994; Kim and Arvan, 1995; Fayadat *et al*., 2000)	Thyroid peroxidase	+	CNX/CRT
Thyroxin-binding globulin deficiency ¶ (Miura *et al*., 1994; Refetoff *et al*., 1996)	Thyroxin-binding globulin	+	
Osteogenesis imperfecta (Lamande and Bateman, 1999)	Type I procollagen	+	
Hereditary hypofibrinogenemia (Roy *et al*., 1996)	Fibrinogen	+	CNX
α1- Antichymotrypsin (ACT) deficiency (Callea *et al*., 1992)	α1- Antichymotrypsin	+	CNX
Neurophyseal diabetes insipidus (Morello *et al*., 2001)	Vasopressin precursor protein	+	CNX, Prolonged Assoc.
Nephrogenic diabetes insipidus (Tamarappoo *et al*., 1999)	Aquaporin II	-	
Charcot-Marie-Tooth disease (Thomas, 1999; Mendell, 1998)	Peripheral myelin protein 22	+	CNX
Pelizaeus-Merzbacher disease (Yool *et al*., 2000; Swanton *et al*., 2003)	Proteolipoprotein	-	CNX, Prolonged Assoc.
Alzheimer disease (Shastry, 2001)	Presenilin	+	CNX
Straussler-Scheinker syndrome (Rudd *et al*., 2001b; Collins *et al*., 2001)	Prion protein processing defect	+	CNX
Hereditary Creutzfeldt-Jacob disease (Rudd *et al*., 2001b; Collins *et al*., 2001)	Prion protein processing defect	+	CNX
von Willebrand Disease	von Willebrand factor (VWF)	+	
Type IIA (Englender *et al*., 1996; Lyons *et al*., 1992)	VWF		
Types I and III (Allen *et al*., 2001)	Types I and III associated VWF variant		CNX/CRT, CNX Prolonged Assoc.
III: Defective transport machinery			
Combined factorsV and VIII deficiency (Nichols *et al*., 1998)	Ergic-53	-	
Spondyloepiphyseal dysplasia tarda (Gedeon *et al*., 1999)	SEDL (sedlin)	-	
Viral Infections: Selected examples that are known to be associated with CNX/CRT quality control			
AIDS (Land and Braakman, 2001)	160/120	+	CNX/CRT
Herpes simplex-1 (Yamashita *et al*., 1996b)	B, C and D	+	CNX/CRT
Cytomegalovirus diseases (Yamashita *et al*., 1996a)	B	+	CNX
Influenza (Hebert *et al*., 1996)	Haemagglutinin	+	CNX/CRT
Hepatitis B (Prange *et al*., 1999)	M	+	CNX
Hepatitis C (Choukhi *et al*., 1998)	E1 and E2	+	CNX/CRT
Rubella (Nakhasi *et al*., 2001)	E1 and E2	+	CNX/CRT
Measles (Bolt, 2001)	Haemagglutinin/Fusion	+	CNX/CRT
Newcastle disease (McGinnes and Morrison, 1998)	Haemagglutinin-neuraminidase	+	CNX
Dengue hemorrhagic fever (Wu *et al*., 2002)	M, E and NS1	+	CNX
Japanese encephalitis (Wu *et al*., 2002)	M, E and NSI	+	CNX
Uukiniemi virus infenction (Veijola and Pettersson, 1999)	G1 and G2	+	CNX/CRT
Vesicular somatitis (Cannon *et al*., 1996)	G	+	CNX/CRT
Unknown consequences$^{\theta\delta}$			
Polycystic liver disease (PCLD, OMIM 174050)$^{\theta}$ (Drenth *et al*., 2003)	Hepatocystin (also indentified as the β-subunit of glucosidase II)	+	CNX/CRT cycle constituent
Congenital disorders of N-glycosylation (CDG)-II b$^{\delta}$ (De Praeter *et al*., 2000)	Glucosidase I and II	+	CNX/CRT cycle constituent

* Please see Aridor and Hannan, 2002 for a more complete list of the ER quality control related diseases. ¶ placed in the first group in Aridor and Hannan, 2000. $^{\theta}$ mutant protein may alter the processing of oligosaccharide chains of various glycoproteins. $^{\delta}$ where the defects are in the trimming and modification of the core oligosaccharide which had already been transferred to the target proteins.

of misfolded glycoproteins to ERAD (Fewell *et al*., 2001; Hampton, 2002; Jarosch *et al*., 2002). For example, the AAA ATPase family members Cdc48 in yeast and p97 in mammals have been shown to be required for the transport of misfolded proteins to the cytosol (Braun *et al*., 2002; Ye *et al*., 2001). As well, ubiquitin ligases (the F-box protein Fbx2 of an ubiquitin ligase complex, SCF (Fbx2) [Yoshida *et al*., 2002], a chaperone-containing ligase, CHIP and E2 [Meacham *et al*., 2001]) have been shown to participate in ERAD of misfolded proteins, suggesting potential links between ubiquitination, ERAD and quality control of glycoproteins (Fewell *et al*., 2001; Hampton, 2002; Jarosch *et al*., 2002). Indeed Qu *et al*. (Qu, *et al*., 1996) have proposed that calnexin itself is polyubiquitinated during ERAD, but this observation has not been confirmed.

Retention, retrieval and ER-associated degradation

In cells which overexpress a temperature sensitive mutant of vesicular somatitis virus G protein, the mutant protein escapes initial ER retention but is retrieved back to the ER bound to the molecular chaperone BiP from the intermediate compartment (IC) and the cis-Golgi network (Hammond *et al*., 1994; Hsu *et al*., 1991). However, the misfolded VSV G mutant protein at the 'exit sites' in the ER is reglucosylated by UGGT and returned to the ER instead of being transported to the Golgi complex (Mezzacasa and Helenius, 2002). Proteins that are localized in the ER possess retention and retrieval signals, including specific C-terminal motifs, such as Lys-Asp-Glu-Leu (KDEL) for soluble proteins (Pelham, 1996) or dilysine (KKxx) motifs for transmembrane proteins (Fiedler *et al*., 1996; Itin *et al*., 1995; Nilsson *et al*., 1989), that mediate the selective retrograde transport of these proteins from the cis-Golgi back to the ER. Furthermore, it has been shown that membrane bound or soluble forms of misfolded proteins are sorted in the ER, either for retention or retrieval, indicating that different recognition mechanisms may exist to target misfolded proteins for degradation (Vashist *et al*., 2001). Moreover, it has been reported that a KDEL-receptor mediated mechanism exists for the retrieval of unassembled subunits of the T-cell antigen receptor to the ER for their eventual disposal (Yamamoto *et al*., 2001).

The presence of glucosidase II, UGGT and calreticulin in pre-Golgi intermediate compartments (Roth *et al*., 2002; Zuber *et al*., 2001) suggests that other compartments of the secretory pathway may also have a role in correct folding and quality control (Roth *et al*., 2002). In addition, endomannosidase, which localizes to the intermediate compartment and has substrate specificity for $Glc_{1-2}Man_9GlcNAc_2$ like glucosidase II, can also act on $Glc_3Man_9GlcNAc_2$ unlike glucosidase II, thus providing an alternative glucosidase II independent pathway (Zuber *et al*., 2000). However, in contrast to glucosidase II, endo-mannosidase can also remove the Glc_1Man residues from monoglucosylated oligosaccharides with trimmed mannose chains (for example, $Glc_1Man_{5-8}GlcNAc_2$-structures), suggesting a role for this enzyme in quality control (Roth *et al*., 2002; Spiro *et al*., 1996). It is proposed that misfolded Man_8-glycoproteins may be released from calreticulin in the intermediate compartment by the action of endomannosidase before their degradation (Zuber *et al*., 2000). It has been speculated that the excessive removal of mannose residues may prevent UGGT-mediated reglucosylation of the misfolded glycoproteins thus diverting misfolded proteins away from CNX/CRT and leading to their degradation (Cabral *et al*., 2001).

The enzymatically "active" and "silent" UGGTs

Recently, UGGT was also identified as a part of the heavy chain-BiP complex including molecular chaperones and folding enzymes BiP, Glucose-regulated protein (GRP)94 (Endoplasmin), GRP170 (an ER heat shock protein 70 family member), an ER Hsp40 cochaperone (ERdj3), and several PDI family members (PDI, ERp72, , CaBP1), cyclophilin B (an ER immunophilin protein) and the SDF2-L1 (an ER stress inducible protein; Meunier *et al*., 2002). The existence of such a network(s) (Kim and Arvan, 1995; Kuznetsov *et al*, 1994; Kuznetsov *et al*, 1997; Tatu and Helenius, 1997) led to a proposal that the ER is organized into different networks containing distinct pool of the ER chaperones (Meunier *et al*., 2002). This might also explain the retention of some molecular chaperone without KDEL sequences in the ER (see in ref. Meunier *et al*., 2002). Such a complex may also explain the sequential/ simultaneous interactions of the molecular chaperones with misfolded proteins (as mentioned above) (Hammond *et al*., 1994). Furthermore, these data suggest that UGGT may well be a part of dynamic molecular chaperone complex, which may also determine the sorting and retrieval of secretory proteins. Such a dynamic network(s) of chaperones could prevent the forward movement of misfolded proteins by their retention (see in ref. Hendershot, 2000). This finding does not rule out the possibility that there are other pools of UGGT not present in the complex (Meunier *et al*., 2002).

UGGT has also been shown to associate with a misfolded variant of α1-antitrypsin (non PiZ; Choudhury *et al*., 1997), ER resident enzymes such as the folding enzyme protein disulfide isomerase (PDI), the chaperone BiP, and carboxylesterase (a specific quality control factor which limits ER export of C-reactive protein; Amouzadeh *et al*., 1997). The enzyme has also been observed in a complex with the selenoprotein, Sep15 (Korotkov *et al*., 2001), which is suggested to play a role in cancer etiology (see in ref. (Korotkov *et al*., 2001). It is speculated that Sep15 may play a role in redox reactions in the complex, which would then have an affect on CNX/CRT-mediated folding. However, UGGT is detected in both selenoprotein-bound and selenoprotein-free forms (Korotkov *et al*., 2001). The physiological significance of UGGT in a complex with selenoproteins and/or other proteins (Amouzadeh *et al*., 1997; Choudhury *et al*., 1997; Korotkov *et al*., 2001; Meunier *et al*., 2002) is yet unclear and is fully functional as a glycosyltransferase *in vitro* in the absence of other proteins.

Two UGGT family members are apparently catalytically inactive: one in human, hUGGT2, (Arnold *et al*., 2000) and one in *S. cerevisiae*, Kre5p (Meaden *et al*., 1990; Figure 2). In *S. cerevisiae* the loss of enzyme activity might be due to the lack of conservation of critical D residues in the C-terminal catalytic domains of these enzymes (Tessier *et al*., 2000) (green boxes, shown with ▸ ◂ in Figure 2).

However, the conservation of these same motifs in the second catalytically inactive UGGT (hUGGT2) sequence suggests additional requirements for the enzyme activity. Comparisons of hUGGT1 and hUGGT2 protein sequences revealed differing residues in the catalytic domain (as identified by a blue ★ under the sequences in Figure 2); these residues may coincide with the loss of activity. Interestingly, three of these four residues also varied in the *S. cerevisiae* Kre5p sequence compared to all other homologues. Additionally, there is divergence within the N-terminus region of hUGGT1 and hUGGT2 which may affect their substrate specificity (Arnold *et al.*, 2000). As well, except first residue, all of these residues differ from all other homologues proteins with *S. cerevisiae* Kre5p sequence. Furthermore, we compared the known inactive UGGT sequences (hUGGT2 and Kre5p) to the known active UGGT sequences (*H. sapiens* UGGT 1, *R. norvegicus*, *D. melanogaster*, and *S. pombe* UGGT proteins), revealing other candidate residues in the catalytic domain (as identified by a red ★ under the sequences in Figure 2).

Remarkably, the catalytically inactive *S. cerevisiae* gene is essential for cell viability (for a recent review, (Parodi, 2000) and appears to function early in the (1,6)-β-D-glucan synthesis pathway (Meaden *et al.*, 1990). Higher eukaryotes (*e.g.* worms, rodents and humans) have evolved two UGGT genes with only one predicted to be catalytically active. An exciting possibility is that the catalytically inactive variants of UGGT including Kre5p are required for the disaggregation of misfolded proteins. At least four possible scenarios for these variants have also been proposed (Arnold *et al.*, 2000) including different substrate specificity, a nucleotide sugar donor other than UDP-glucose, targeting a substrate for degradation, or binding of catalytically inactive hUGGT 2 to an unknown protein partner which would then elicit a gain of UGGT enzyme activity. Since, the enzymatically inactive EDEM (Hosokawa *et al.*, 2001; Jakob *et al.*, 2001a; Nakatsukasa *et al.*, 2001) has been linked to quality control (Molinari *et al.*, 2003; Oda *et al.*, 2003) and ERp57 displays increased isomerase activity when associated with calnexin (Oliver *et al.*, 1997; Zapun *et al.*, 1998), this then raises the possibility of a role for the enzymatically "silent" UGGTs in quality control.

Quality control implications for diseases

Many human diseases can be classified as "protein trafficking diseases" where mutant secretory proteins are subjected to the ER quality control system and its associated ERAD (Amara *et al.*, 1992; Aridor and Balch, 1999; Kim and Arvan, 1998; Kopito, 1999; Olkkonen and Ikonen, 2000; Thomas *et al.*, 1995) (Table 1). These can be divided into three groups (I, II, and III, Table 1). The first group of diseases corresponds to loss of coupling to the ER export machinery leading to degradation of misfolded proteins. The second group of diseases correlates with ER accumulation of mutant proteins that are uncoupled from the ER export machinery and fail to be degraded and forms aggregates in the ER. The third group of diseases is due to defects in the machinery required for transport from the ER to the Golgi complex (Aridor and Balch, 1999; Aridor and Hannan, 2000). In addition, viral and bacterial pathogens manipulate ER function for their immunological survival (Land and Braakman, 2001; Ploegh, 1998; Rust *et al.*, 2001; Yamashita *et al.*, 1996a) or to deliver their toxic products to the cytosol (Lord and Roberts, 1998). Viral infections are often linked to massive production of viral proteins and their accumulation in the ER (Aridor and Balch, 1999; Ploegh, 1998).

Mutant glycoproteins associated with protein trafficking diseases are also shown in Table 1 (Amara *et al.*, 1992; Aridor and Balch, 1999; Kopito, 1999). The majorities of these proteins interact with calnexin and/or calreticulin and therefore are also potential substrates for UGGT. It is inferred that UGGT and its reglucosylation of mutant proteins is responsible for rebinding to CNX/CRT (for example, vesicular stomatitis virus G (Peterson and Helenius, 1999), hemagglutinin (Peterson and Helenius, 1999), α_1-antitrypsin (Choudhury, 1997), thyroglobulin (Parker *et al.*, 1995) (Table 1), subunits of the T cell receptor (Gardner and Kearse, 1999).

From a therapeutic perspective, the problem of inherited protein misfolding is being addressed by several related strategies: One approach is based on attempts to chaperone misfolded proteins into a native-like structure that can evade the ER quality control machinery using either biological or chemical chaperones (Chow *et al.*, 2001; Loo and Clarke, 1997). In another approach, to the accumulation of a mutant variant (PiZ) that is mostly retained in the ER (Qu *et al.*, 1997) osmolytes such as trimethylamine-N-oxide and sarcosine significantly reduce the rate of α_1-antitrypsin mutant polymerization with no effect on the normal inhibitory function of α_1-antitrypsin for serine proteases (Chow *et al.*, 2001).

The other approach focuses on circumventing the quality control machinery of the ER, allowing proteins to be secreted, irrespective of their structural abnormalities (Burrows *et al.*, 2000; Choo-Kang and Zeitlin, 2001; Rubenstein *et al.*, 1997). The relevant example of this approach is the transmembrane conductance regulator protein (CFTR). The CFTR ΔF508 mutant is the most common cystic fibrosis allele and the mutated but otherwise functionally active protein is thus retained in the ER and eventually targeted for degradation, rather than being transported to the plasma membrane (Kopito and Ron, 2000; Kopito, 1999). The use of 4-phenylbutyrate (4PBA) increases the expression of the ΔF508-CFTR mutant to the plasma membrane (Rubenstein *et al.*, 1997), possibly acting through a cytosolic molecular chaperone, Hsp70 (Choo-Kang and Zeitlin, 2001). The use of specific mannosidase inhibitors may also been relevant to overcome the increased degradation and mislocation of mutant α_1-antitrypsin (Marcus and Perlmutter, 2000).

Competitive or noncompetitive inhibition of UGGT, leading to inhibition of the CNX/CRT cycle, may be an alternative approach to development of therapies for protein misfolding diseases (see ref. Kopito and Ron, 2000). Although no specific inhibitors of this enzyme are known, related inhibitors may prove valuable to dissect a UGGT link to the diseases listed in Table 1 (Block and Jordan, 2001; Dwek *et al.*, 2002). It is expected that mutation or

removal of UGGT genes as well as components of the CNX/CRT cycle in mouse models of the diseases indicated in Table 1 will provide further insight into new targets.

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References

Allen, S., A.C. Goodeve, I.R. Peake, and M.E. Daly. 2001. Endoplasmic reticulum retention and prolonged association of a von Willebrand's disease-causing von Willebrand factor variant with ERp57 and calnexin. Biochem. Biophys. Res Commun. 280:448-53.

Amara, J., S. Cheng, and A. Smith. 1992. Intracellular protein trafficking defects in human disease. Trends in Cell Biology. 2:145-149.

Amouzadeh, H., M. Bourdi, J. Martin, B. Martin, and L. Pohl. 1997. UDP-glucose:glycoprotein glucosyltransferase associates with endoplasmic reticulum chaperones and its activity is decreased *in vivo* by the inhalation anesthetic halothane. Chem. Res. Toxicol. 10:59-63.

Amselem, S., M. Sobrier, P. Duquesnoy, R. Rappaport, M. Postel-Vinay, M. Gourmelen, B. Dallapiccola, and M. Goossens. 1991. Recurrent nonsense mutations in the growth hormone receptor from patients with Laron dwarfism. J. Clin. Invest. 87:1098-102.

Aridor, M., and W. Balch. 1999. Integration of endoplasmic reticulum signaling in health and disease. Nat. Med. 5:745-51.

Aridor, M., and L.A. Hannan. 2000. Traffic jam: a compendium of human diseases that affect intracellular transport processes. Traffic. 1:836-51.

Aridor, M., and L.A. Hannan. 2002. Traffic jams II: an update of diseases of intracellular transport. Traffic. 3:781-90.

Arnold, S., L. Fessler, J. Fessler, and R. Kaufman. 2000. Two homologues encoding human UDP-glucose:glycoprotein glucosyltransferase differ in mRNA expression and enzymatic activity. Biochemistry. 39:2149-63.

Bass, J., G. Chiu, Y. Argon, and D.F. Steiner. 1998. Folding of insulin receptor monomers is facilitated by the molecular chaperones calnexin and calreticulin and impaired by rapid dimerization. J. Cell Biol. 141:637-646.

Ben-Zeev, O., H.Z. Mao, and M.H. Doolittle. 2002. Maturation of lipoprotein lipase in the endoplasmic reticulum. Concurrent formation of functional dimers and inactive aggregates. J. Biol. Chem. 277:10727-10738.

Bergeron, J., M. Brenner, D. Thomas, and D. Williams. 1994. Calnexin: a membrane-bound chaperone of the endoplasmic reticulum. Trends Biochem. Sci. 19:124-8.

Block, T.M., and R. Jordan. 2001. Iminosugars as possible broad spectrum anti hepatitis virus agents: the glucovirs and alkovirs. Antivir. Chem. Chemother. 12:317-25.

Blond-Elguindi, S., A.M. Fourie, J.F. Sambrook, and M.J. Gething. 1993. Peptide-dependent stimulation of the ATPase activity of the molecular chaperone BiP is the result of conversion of oligomers to active monomers. J. Biol. Chem. 268:12730-5.

Bolt, G. 2001. The measles virus (MV) glycoproteins interact with cellular chaperones in the endoplasmic reticulum and MV infection upregulates chaperone expression. Archives of Virology. 146: 2055-2068.

Bonen, D.K., F. Nassir, A.M.L. Hausman, and N.O. Davidson. 1998. Inhibition of N-linked glycosylation results in retention of intracellular apo[a] in hepatoma cells, although nonglycosylated and immature forms of apolipoprotein[a] are competent to associate with apolipoprotein B-100 *in vitro*. J. Lipid Res. 39:1629-1640.

Brada, D., and U.C. Dubach. 1984. Isolation of a homogeneous glucosidase II from pig kidney microsomes. Eur. J. Biochem. 141:149-56.

Braun, S., K. Matuschewski, M. Rape, S. Thoms, and S. Jentsch. 2002. Role of the ubiquitin-selective CDC48UFD1/NPL4 chaperone (segregase) in ERAD of OLE1 and other substrates. EMBO J. 21:615-621.

Breton, C., E. Bettler, D. Joziasse, R. Geremia, and A. Imberty. 1998. Sequence-function relationships of prokaryotic and eukaryotic galactosyltransferases. J. Biochem. 123:1000-9.

Burda, P., and M. Aebi. 1999. The dolichol pathway of N-linked glycosylation. Biochim. Biophys. Acta. 1426:239-57.

Burrows, J.A.J., L.K. Willis, and D.H. Perlmutter. 2000. Chemical chaperones mediate increased secretion of mutant alpha 1-antitrypsin (alpha 1-AT) Z: A potential pharmacological strategy for prevention of liver injury and emphysema in alpha 1-AT deficiency. PNAS. 97:1796-1801.

Cabral, C., Y. Liu, and R. Sifers. 2001. Dissecting glycoprotein quality control in the secretory pathway. Trends Biochem. Sci. 26:619-24.

Callea, F., M. Brisigotti, G. Fabbretti, F. Bonino, and V. Desmet. 1992. Hepatic endoplasmic reticulum storage diseases. Liver. 12:357-62.

Campbell, J., G. Davies, V. Bulone, and B. Henrissat. 1997. A classification of nucleotide-diphospho-sugar glycosyltransferases based on amino acid sequence similarities. Biochem. J. 326:929-39.

Cannon, K.S., D.N. Hebert, and A. Helenius. 1996. Glycan-dependent and -independent association of Vesicular Stomatitis Virus G protein with calnexin. J. Biol. Chem. 271:14280-14284.

Caramelo, J.J., O.A. Castro, L.G. Alonso, G. De Prat-Gay, and A.J. Parodi. 2003. UDP-Glc:glycoprotein glucosyltransferase recognizes structured and solvent accessible hydrophobic patches in molten globule-like folding intermediates. Proc. Natl. Acad. Sci. U S A. 100:86-91.

Choo-Kang, L.R., and P.L. Zeitlin. 2001. Induction of HSP70 promotes {Delta}F508 CFTR Trafficking. Am. J. Physiol. Lung Cell Mol. Physiol. 281:L58-68.

Choudhury, P., Y. Liu, R.J. Bick, and R.N. Sifers. 1997. Intracellular association between UDP-glucose:glycoprotein glucosyltransferase and an incompletely folded variant of alpha 1-antitrypsin. J. Biol. Chem. 272:13446-13451.

Choukhi, A., S. Ung, C. Wychowski, and J. Dubuisson. 1998. Involvement of endoplasmic reticulum chaperones in the folding of hepatitis C virus glycoproteins. J. Virol. 72:3851-3858.

Chow, M., G. Devlin, and S. Bottomley. 2001. Osmolytes as modulators of conformational changes in serpins. Biol. Chem. 382:1593-9.

Coakley, R., C. Taggart, S. O'Neill, and N. McElvaney. 2001. Alpha1-antitrypsin deficiency: biological answers to clinical questions. Am. J. Med. Sci. 321:33-41.

Collins, S., C. McLean, and C. Masters. 2001. Gerstmann-Straussler-Scheinker syndrome,fatal familial insomnia, and kuru: a review of these less common human transmissible spongiform encephalopathies. J. Clin. Neurosci. 8:387-97.

de Carvalho, D.P., K.G. Rego, and D. Rosenthal. 1994. Thyroid peroxidase in dyshormonogenetic goiters with organification and thyroglobulin defects. Thyroid. 4:421-6.

De Praeter, C.M., G.J. Gerwig, E. Bause, L.K. Nuytinck, J.F. Vliegenthart, W. Breuer, J.P. Kamerling, M.F. Espeel, J.J. Martin, A.M. De Paepe, N.W. Chan, G.A. Dacremont, and R.N. Van Coster. 2000. A novel disorder caused by defective biosynthesis of N-linked oligosaccharides due to glucosidase I deficiency. Am. J. Hum. Genet. 66: 1744-1756.

Deutsch, C. 2002. Potassium channel ontogeny. Annu. Rev. Physiol. 64:19-46.

Doerrler, W.T., and M.A. Lehrman. 1999. Regulation of the dolichol pathway in human fibroblasts by the endoplasmic reticulum unfolded protein response. PNAS. 96:13050-13055.

Drenth, J.P., R.H. te Morsche, R. Smink, J.S. Bonifacino, and J.B. Jansen. 2003. Germline mutations in PRKCSH are associated with autosomal dominant polycystic liver disease. Nat. Genet. 33: 345-347.

Dwek, R., T. Butters, F. Platt, and N. Zitzmann. 2002. Targeting glycosylation as a therapeutic approach. Nature Reviews Drug Discovery. 1:65-75.

Englender, T., A. Lattuada, P.M. Mannucci, J.E. Sadler, and A. Inbal. 1996. Analysis of Arg834Gln and Val902Glu type 2A von Willebrand disease mutations: studies with recombinant von Willebrand factor and correlation with patient characteristics. Blood. 87:2788-94.

Fayadat, L., S. Siffroi-Fernandez, J. Lanet, and J.-L. Franc. 2000. Calnexin and calreticulin binding to human thyroperoxidase is required for its first folding step(s) but is not sufficient to promote efficient cell surface expression. Endocrinology. 141:959-966.

Fernandez, F., S. Trombetta, U. Hellman, and A. Parodi. 1994. Purification to homogeneity of UDP-glucose:glycoprotein glucosyltransferase from Schizosaccharomyces pombe and apparent absence of the enzyme from Saccharomyces cerevisiae. J. Biol. Chem. 269:30701-6.

Fewell, S.W., K.J. Travers, J.S. Weissman, and J.L. Brodsky. 2001. The action of molecular chaperones in the early secretory pathway. Annu. Rev. Genet. 35:149-191.

Fiedler, K., M. Veit, M. Stamnes, and J. Rothman. 1996. Bimodal interaction of coatomer with the p24 family of putative cargo receptors. Science. 273:1396-9.

Frederick, J.M., N.V. Krasnoperova, K. Hoffmann, J. Church-Kopich, K. Ruther, K. Howes, J. Lem, and W. Baehr. 2001. Mutant rhodopsin transgene expression on a null background. Invest. Ophthalmol. Vis. Sci. 42: 826-833.

Furutani, M., M.C. Trudeau, N. Hagiwara, A. Seki, Q. Gong, Z. Zhou, S. Imamura, H. Nagashima, H. Kasanuki, A. Takao, K. Momma, C.T. January, G.A. Robertson, and R. Matsuoka. 1999. Novel mechanism associated with an inherited cardiac arrhythmia: defective protein Trafficking by the mutant HERG (G601S) potassium channel. Circulation. 99:2290-4.

Gardner, T.G., and K.P. Kearse. 1999. Modification of the T cell antigen receptor (TCR) complex by UDP-glucose:glycoprotein glucosyltransferase. TCR folding is finalized convergent with formation of alpha beta delta epsilon gamma epsilon complexes. J. Biol. Chem. 274:14094-14099.

Garfield, N., and A. Karaplis. 2001. Genetics and animal models of hypoparathyroidism. Trends Endocrinol. Metab. 12:288-94.

Gedeon, A.K., A. Colley, R. Jamieson, E.M. Thompson, J. Rogers, D. Sillence, G.E. Tiller, J.C. Mulley, and J. Gecz. 1999. Identification of the gene (SEDL) causing X-linked spondyloepiphyseal dysplasia tarda. Nat. Genet. 22:400-4.

Grinna, L.S., and P.W. Robbins. 1980. Substrate specificities of rat liver microsomal glucosidases which process glycoproteins. J. Biol. Chem. 255:2255-8.

Guerin, M. and A. J. Parodi. 2003. The UDP-glucose:glycoprotein glucosyltransferase is organized in at least two tightly bound domains from yeast to mammals. J. Biol. Chem. 278: 20540-6.

Halaban, R., E. Cheng, Y. Zhang, G. Moellmann, D. Hanlon, M. Michalak, V. Setaluri, and D.N. Hebert. 1997. Aberrant retention of tyrosinase in the endoplasmic reticulum mediates accelerated degradation of the enzyme and contributes to the dedifferentiated phenotype of amelanotic melanoma cells. PNAS. 94:6210-6215.

Halaban, R., R.S. Patton, E. Cheng, S. Svedine, E.S. Trombetta, M.L. Wahl, S. Ariyan, and D.N. Hebert. 2002. Abnormal acidification of melanoma cells induces tyrosinase retention in the early secretory pathway. J. Biol. Chem. 277:14821-14828.

Hammond, C., I. Braakman, and A. Helenius. 1994. Role of N-linked oligosaccharide recognition, glucose trimming, and calnexin in glycoprotein folding and quality control. PNAS. 91:913-917.

Hampton, R.Y. 2002. ER-associated degradation in protein quality control and cellular regulation. Curr. Opin. Cell Biol. 14:476-82.

Hebert, D., B. Foellmer, and A. Helenius. 1995. Glucose trimming and reglucosylation determine glycoprotein association with calnexin in the endoplasmic reticulum. Cell. 81:425-33.

Hebert, D., B. Foellmer, and A. Helenius. 1996. Calnexin and calreticulin promote folding, delay oligomerization and suppress degradation of influenza hemagglutinin in microsomes. EMBO J. 15:2961-8.

Helenius, A., E.S. Trombetta, D.N. Hebert, and J.F. Simons. 1997. Calnexin, calreticulin and the folding of glycoproteins. Trends in Cell Biology. 7:193-200.

Hendershot, L.M. 2000. Giving protein traffic the green light. Nat. Cell Biol. 2:E105-6.

Hettkamp, H., G. Legler, and E. Bause. 1984. Purification by affinity chromatography of glucosidase I, an endoplasmic reticulum hydrolase involved in the processing of asparagine-linked oligosaccharides. Eur. J. Biochem. 142:85-90.

Hosokawa, N., I. Wada, K. Hasegawa, T. Yorihuzi, L. Tremblay, A. Herscovics, and K. Nagata. 2001. A novel ER alpha-mannosidase-like protein accelerates ER-associated degradation. EMBO Rep. 2:415-22.

Hsu, V., L. Yuan, J. Nuchtern, J. Lippincott-Schwartz, G. Hammerling, and R. Klausner. 1991. A recycling pathway between the endoplasmic reticulum and the Golgi apparatus for retention of unassembled MHC class I molecules. Nature. 352:441-4.

Illing, M.E., R.S. Rajan, N.F. Bence, and R.R. Kopito. 2002. A rhodopsin mutant linked to autosomal dominant retinitis pigmentosa is prone tp aggregate and interacts with the ubiquitin proteasome system. J. Biol. Chem. 277: 34150-34160.

Ishii, S., Y. Suzuki, and J.Q. Fan. 2000. Role of Ser-65 in the activity of alpha-galactosidase A: characterization of a point mutation (S65T) detected in a patient with Fabry disease. Arch. Biochem. Biophys. 377:228-33.

Itin, C., R. Schindler, and H. Hauri. 1995. Targeting of protein ERGIC-53 to the ER/ERGIC/cis-Golgi recycling pathway. J Cell Biol. 131:57-67.

Jakob, C., D. Bodmer, U. Spirig, P. Battig, A. Marcil, D. Dignard, J. Bergeron, D. Thomas, and M. Aebi. 2001a. Htm1p, a mannosidase-like protein, is involved in glycoprotein degradation in yeast. EMBO Rep. 2:423-30.

Jakob, C.A., E. Chevet, D.Y. Thomas, and J.J. Bergeron. 2001b. Lectins of the ER quality control machinery. Results Probl. Cell Differ. 33:1-17.

Jarosch, E., R. Geiss-Friedlander, B. Meusser, J. Walter, and T. Sommer. 2002. Protein dislocation from the endoplasmic reticulum—pulling out the suspect. Traffic. 3:530-6.

Jelinek-Kelly, S., and A. Herscovics. 1988. Glycoprotein biosynthesis in Saccharomyces cerevisiae. Purification of the alpha-mannosidase which removes one specific mannose residue from Man9GlcNAc. J. Biol. Chem. 263:14757-63.

Jorgensen, M.M., O.N. Jensen, H.U. Holst, J.-J. Hansen, T.J. Corydon, P. Bross, L. Bolund, and N. Gregersen. 2000. Grp78 Is Involved in Retention of Mutant Low Density Lipoprotein Receptor Protein in the Endoplasmic Reticulum. J. Biol. Chem. 275:33861-33868.

Kaback, M., and R. Desnick. 2001. Tay-Sachs disease: from clinical description to molecular defect. Adv. Genet. 44:1-9.

Kim, P., and P. Arvan. 1995. Calnexin and BiP act as sequential molecular chaperones during thyroglobulin folding in the endoplasmic reticulum. J. Cell Biol. 128:29-38.

Kim, P.S., and P. Arvan. 1998. Endocrinopathies in the family of endoplasmic reticulum (ER) storage diseases: Disorders of protein trafficking and the role of ER molecular chaperones. Endocr. Rev. 19:173-202.

Kopito, R., and D. Ron. 2000. Conformational disease. Nat. Cell Biol. 2:E207-9.

Kopito, R.R. 1999. Biosynthesis and degradation of CFTR. Physiol. Rev. 79:167-173.

Kornfeld, R., and S. Kornfeld. 1985. Assembly of asparagine-linked oligosaccharides. Annu. Rev. Biochem. 54:631-64.

Korotkov, K.V., E. Kumaraswamy, Y. Zhou, D.L. Hatfield, and V.N. Gladyshev. 2001. Association between the 15-kDa selenoprotein and UDP-glucose:glycoprotein glucosyltransferase in the endoplasmic reticulum of mammalian cells. J. Biol. Chem. 276:15330-15336.

Kuznetsov, G., L. B. Chen, *et al*. 1994. Several endoplasmic reticulum stress proteins, including ERp72, interact with thyroglobulin during its maturation. J. Biol. Chem. 269: 22990-5.

Kuznetsov, G., L. B. Chen, *et al*. 1997. Multiple molecular chaperones complex with misfolded large oligomeric glycoproteins in the endoplasmic reticulum. J. Biol. Chem. 272: 3057-63.

Kühn, L.C. 1999. Iron overload: molecular clues to its cause. Trends in Biochemical Sciences. 24:164-166.

Labriola, C., J.J. Cazzulo, and A.J. Parodi. 1999. Trypanosoma cruzi calreticulin is a lectin that binds monoglucosylated oligosaccharides but not protein moieties of glycoproteins. Mol. Biol. Cell. 10:1381-1394.

Lamande, S., and J. Bateman. 1999. Procollagen folding and assembly: the role of endoplasmic reticulum enzymes and molecular chaperones. Semin Cell Dev. Biol. 10:455-64.

Land, A., and I. Braakman. 2001. Folding of the human immunodeficiency virus type 1 envelope glycoprotein in the endoplasmic reticulum. Biochimie. 83:783-790.

Le, A., J. Steiner, G. Ferrell, J. Shaker, and R. Sifers. 1994. Association between calnexin and a secretion-incompetent variant of human alpha 1-antitrypsin.: J. Biol. Chem. 269:7514-9.

Lodish, H.F., N. Kong, M. Snider, and G.J. Strous. 1983. Hepatoma secretory proteins migrate from rough endoplasmic reticulum to Golgi at characteristic rates. Nature. 304:80-3.

Loo, T.W., and D.M. Clarke. 1997. Identification of residues in the drug-binding site of human P-glycoprotein using a thiol-reactive substrate. J. Biol. Chem. 272:31945-31948.

Lord, J.M., and Roberts, LM. 1998. Toxin Entry: Retrograde Transport through the secretory pathway. J. Cell Biol. 140:733-736.

Lyons, S.E., M.E. Bruck, E.J. Bowie, and D. Ginsburg. 1992. Impaired intracellular transport produced by a subset of type IIA von Willebrand disease mutations. J. Biol. Chem. 267:4424-30.

Marcus, N.Y., and D.H. Perlmutter. 2000. Glucosidase and mannosidase inhibitors mediate increased secretion of mutant alpha 1 antitrypsin Z. J. Biol. Chem. 275:1987-1992.

McGinnes, L.W., and T.G. Morrison. 1998. Role of carbohydrate processing and calnexin binding in the folding and activity of the HN protein of Newcastle disease virus. Virus Research. 53:175-185.

Meacham, G.C., C. Patterson, W. Zhang, J.M. Younger, and D.M. Cyr. 2001. The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation. Nat. Cell Biol. 3:100-5.

Meaden, P., K. Hill, J. Wagner, D. Slipetz, S. Sommer, and H. Bussey. 1990. The yeast KRE5 gene encodes a probable endoplasmic reticulum protein required for (1-6)-beta-D-glucan synthesis and normal cell growth. Mol. Cell Biol. 10:3013-9.

Mendell, J. 1998. Charcot-Marie-Tooth neuropathies and related disorders. Semin. Neurol. 18:41-7.

Meunier, L., Y.K. Usherwood, K.T. Chung, and L.M. Hendershot. 2002. A subset of chaperones and folding enzymes form multiprotein complexes in endoplasmic reticulum to bind nascent proteins. Mol. Biol. Cell. 13:4456-69.

Mezzacasa, A., and A. Helenius. 2002. The transitional ER defines a boundary for quality control in the secretion of tsO45 VSV glycoprotein. Traffic. 3:833-49.

Michalak, M., E. Corbett, N. Mesaeli, K. Nakamura, and M. Opas. 1999. Calreticulin: one protein, one gene, many functions. Biochem. J. 344:281-92.

Miura, Y., F. Kambe, I. Yamamori, Y. Mori, Y. Tani, Y. Murata, Y. Oiso, and H. Seo. 1994. A truncated thyroxine-binding globulin due to a frameshift mutation is retained within the rough endoplasmic reticulum: a possible mechanism of complete thyroxine-binding globulin deficiency in Japanese. J. Clin. Endocrinol. Metab. 78:283-7.

Molinari, M. and A. Helenius. 1999. Glycoproteins form mixed disulphides with oxidoreductases during folding in living cells. Nature 402: 90-3.

Molinari, M., V. Calanca, C. Galli, P. Lucca, and P. Paganetti. 2003. Role of EDEM in the release of misfolded glycoproteins from the calnexin cycle. Science. 299:1397-400.

Molinari, M., C. Galli, V. Piccaluga, M. Pieren, and P. Paganetti. 2002. Sequential assistance of molecular chaperones and transient formation of covalent complexes during protein degradation from the ER. J. Cell Biol. 158:247-57.

Molinari, M., and A. Helenius. 2000. Chaperone selection during glycoprotein translocation into the endoplasmic reticulum. Science. 288:331-333.

Morello, J., A. Salahpour, U. Petaja-Repo, A. Laperriere, M. Lonergan, M. Arthus, I. Nabi, D. Bichet, and M. Bouvier. 2001. Association of calnexin with wild type and mutant AVPR2 that causes nephrogenic diabetes insipidus. Biochemistry. 40:6766-75.

Naim, H., J. Roth, E. Sterchi, M. Lentze, P. Milla, J. Schmitz, and H. Hauri. 1988. Sucrase-isomaltase deficiency in humans. Different mutations disrupt intracellular transport, processing, and function of an intestinal brush border enzyme. J. Clin. Invest. 82:667-79.

Nakatsukasa, K., S.-i. Nishikawa, N. Hosokawa, K. Nagata, and T. Endo. 2001. Mnl1p, an alpha -mannosidase-like protein in yeast Saccharomyces cerevisiae, is required for Endoplasmic reticulum-associated degradation of glycoproteins. J. Biol. Chem. 276:8635-8638.

Nakhasi, H., M. Ramanujam, C. Atreya, T. Hobman, N. Lee, A. Esmaili, and R. Duncan. 2001. Rubella virus glycoprotein interaction with the endoplasmic reticulum calreticulin and calnexin. Arch Virol. 146:1-14.

Nauseef, W. 1999. Quality control in the endoplasmic reticulum: lessons from hereditary myeloperoxidase deficiency. J. Lab. Clin. Med. 134:215-21.

Nauseef, W.M., S.J. McCormick, and M. Goedken. 1998. Coordinated participation of calreticulin and calnexin in the biosynthesis of myeloperoxidase. J. Biol. Chem. 273:7107-7111.

Nichols, W., U. Seligsohn, A. Zivelin, V. Terry, C. Hertel, M. Wheatley, M. Moussalli, H. Hauri, N. Ciavarella, R. Kaufman, and D. Ginsburg. 1998. Mutations in the ER-Golgi intermediate compartment protein ERGIC-53 cause combined deficiency of coagulation factors V and VIII. Cell. 93:61-70.

Nilsson, T., M. Jackson, and P. Peterson. 1989. Short cytoplasmic sequences serve as retention signals for transmembrane proteins in the endoplasmic reticulum. Cell. 58:707-18.

Oda, Y., N. Hosokawa, I. Wada, and K. Nagata. 2003. EDEM as an acceptor of terminally misfolded glycoproteins released from calnexin. Science. 299:1394-7.

Oliver, J.D., F.J. van der Wal, N.J. Bulleid, and S. High. 1997. Interaction of the thiol-dependent reductase ERp57 with nascent glycoproteins. Science. 275:86-88.

Olkkonen, V., and E. Ikonen. 2000. Genetic defects of intracellular-membrane transport. New Engl. J. Med. 343:1095-104.

Ou, W., P. Cameron, D. Thomas, and J. Bergeron. 1993. Association of folding intermediates of glycoproteins with calnexin during protein maturation. Nature. 364:771-6.

Parker, C.G., L.I. Fessler, R.E. Nelson, and J.H. Fessler. 1995. Drosophila UDP-glucose:glycoprotein glucosyltransferase: sequence and characterization of an enzyme that distinguishes between denatured and native proteins. EMBO J. 14:1294-303.

Parodi, A., and J. Cazzulo. 1982. Protein glycosylation in Trypanosoma cruzi. II. Partial characterization of protein-bound oligosaccharides labeled "*in vivo*". J. Biol. Chem. 257:7641-5.

Parodi, A.J. 2000. Protein glucosylation and its role in protein folding. Annu. Rev. Biochem. 69:69-93.

Pelham, H. 1996. The dynamic organisation of the secretory pathway. Cell Struct. Funct. 21:413-9.

Pelletier, M.F., A. Marcil, G. Sevigny, C.A. Jakob, D.C. Tessier, E. Chevet, R. Menard, J.J. Bergeron, and D.Y. Thomas. 2000. The heterodimeric structure of glucosidase II is required for its activity, solubility, and localization *in vivo*. Glycobiology. 10:815-27.

Peterson, J., and A. Helenius. 1999. *In vitro* reconstitution of calreticulin-substrate interactions. J. Cell Sci. 112:2775-2784.

Pilon, M., R. Schekman, and K. Romisch. 1997. Sec61p mediates export of a misfolded secretory protein from the endoplasmic reticulum to the cytosol for degradation. EMBO J. 16:4540-4548.

Pind, S., J. Riordan, and D. Williams. 1994. Participation of the endoplasmic reticulum chaperone calnexin (p88, IP90) in the biogenesis of the cystic fibrosis transmembrane conductance regulator. J. Biol. Chem. 269:12784-8.

Ploegh, H.L. 1998. Viral strategies of immune evasion. Science. 280:248-253.

Prange, R., M. Werr, and H. Loffler-Mary. 1999. Chaperones involved in hepatitis B virus morphogenesis. Biol. Chem. 380:305-14.

Qu, D., J. Teckman, and D. Perlmutter. 1997. Review: alpha 1-antitrypsin deficiency associated liver disease. J. Gastroenterol. Hepatol. 12:404-16.

Qu, D., J. H. Teckman, *et al.* 1996. Degradation of a Mutant Secretory Protein, alpha 1-Antitrypsin Z, in the Endoplasmic Reticulum Requires Proteasome Activity. J. Biol. Chem. 271(37): 22791-22795.

Refetoff, S., Y. Murata, Y. Mori, O.E. Janssen, K. Takeda, and Y. Hayashi. 1996. Thyroxine-binding globulin: organization of the gene and variants. Horm. Res. 45:128-38.

Reznik, S., and L. Fricker. 2001. Carboxypeptidases from A to Z: implications in embryonic development and Wnt binding. Cell Mol. Life Sci. 58:1790-804.

Ritter, C., and A. Helenius. 2000. Recognition of local glycoprotein misfolding by the ER folding sensor UDP-glucose:glycoprotein glucosyltransferase. Nat. Struct. Biol. 7:278-80.

Rodan, A.R., J.F. Simons, E.S. Trombetta, and A. Helenius. 1996. N-linked oligosaccharides are necessary and sufficient for association of glycosylated forms of bovine RNase with calnexin and calreticulin. EMBO J. 15:6921-30.

Roth, J., C. Zuber, B. Guhl, J. Fan, and M. Ziak. 2002. The importance of trimming reactions on asparagine-linked oligosaccharides for protein quality control. Histochem. Cell Biol. 117:159-69.

Roy, S., A. Sun, and C. Redman. 1996. *In vitro* assembly of the component chains of fibrinogen requires endoplasmic reticulum factors. J. Biol. Chem. 271:24544-24550.

Rubenstein, R.C., M.E. Egan, and P.L. Zeitlin. 1997. *In vitro* pharmacologic restoration of CFTR-mediated chloride transport with sodium 4-phenylbutyrate in cystic fibrosis epithelial cells containing delta F508-CFTR. J. Clin. Invest. 100:2457-2465.

Rudd, P., G. Opdenakker, and R. Dwek. 2001a. Holistic approaches to glycobiology. Nat. Biotechnol. 19:531-2.

Rudd, P., M. Wormald, D. Wing, S. Prusiner, and R. Dwek. 2001b. Prion glycoprotein: structure, dynamics, and roles for the sugars. Biochemistry. 40:3759-66.

Rudd, P.M., T. Elliott, P. Cresswell, I.A. Wilson, and R.A. Dwek. 2001c. Glycosylation and the immune system. Science. 291:2370-2376.

Rust, R.C., L. Landmann, R. Gosert, B.L. Tang, W. Hong, H.-P. Hauri, D. Egger, and K. Bienz. 2001. Cellular COPII proteins are involved in production of the vesicles that form the poliovirus replication complex. J. Virol. 75:9808-9818.

Saliba, R.S., P.M.G. Munro, P.J. Luthert, and M.E. Cheetham. 2002. The cellular fate of mutant rhodopsin: quality control, degradation and aggresome formation. J. Cell Sci. 115: 2907-2918.

Sampietro, M., and A. Iolascon. 1999. Molecular pathology of Crigler-Najjar type I and II and Gilbert's syndromes. Haematologica. 84:150-7.

Schrag, J.D., B. J.J., Y. Li, S. Borisova, M. Hahn, D.Y. Thomas, and M. Cygler. 2001. The Structure of calnexin, an ER chaperone involved in quality control of protein folding. Mol. Cell. 8:633-44.

Shastry, B. 2001. Molecular and cell biological aspects of Alzheimer disease. J. Hum. Genet. 46:609-18.

Silberstein, S., and R. Gilmore. 1996. Biochemistry, molecular biology, and genetics of the oligosaccharyltransferase. FASEB J. 10:849-58.

Sousa, M., M. Ferrero-Garcia, and A. Parodi. 1992. Recognition of the oligosaccharide and protein moieties of glycoproteins by the UDP-Glc:glycoprotein glucosyltransferase. Biochemistry. 31:97-105.

Sousa, M., and A. Parodi. 1995. The molecular basis for the recognition of misfolded glycoproteins by the UDP-Glc:glycoprotein glucosyltransferase. EMBO J. 14:4196-203.

Spiro, R.G., Q. Zhu, V. Bhoyroo, and H.-D. Söling. 1996. Definition of the lectin-like properties of the molecular chaperone, calreticulin, and demonstration of its copurification with endomannosidase from rat liver Golgi. J. Biol. Chem. 271:11588-11594.

Suh, K., J.E. Bergmann, and C.A. Gabel. 1989. Selective retention of monoglucosylated high mannose oligosaccharides by a class of mutant vesicular stomatitis virus G proteins. J. Cell Biol. 108:811-9.

Swanton, E., S. High, and P. Woodman. 2003. Role of calnexin in the glycan-independent quality control of proteolipid protein. EMBO J. 22: 2948-2958.

Tamarappoo, B.K., B. Yang, and A.S. Verkman. 1999. Misfolding of mutant aquaporin-2 water channels in nephrogenic Diabetes Insipidus. J. Biol. Chem. 274:34825-34831.

Tatu, U. and A. Helenius 1997. Interactions between newly synthesized glycoproteins, calnexin and a network of resident chaperones in the endoplasmic reticulum. J. Cell Biol. 136: 555-65.

Taylor, S.C., P. Thibault, D.C. Tessier, J.J. Bergeron, and D.Y. Thomas. 2003. Glycopeptide specificity of the secretory protein folding sensor UDP-glucose glycoprotein:glucosyltransferase. EMBO Rep. 4:405-11.

Tessier, D., D. Dignard, A. Zapun, A. Radominska-Pandya, A. Parodi, J. Bergeron, and D. Thomas. 2000. Cloning and characterization of mammalian UDP-glucose glycoprotein: glucosyltransferase and the development of a specific substrate for this enzyme. Glycobiology. 10:403-12.

Thomas, P.J., B.-H. Qu, and P.L. Pedersen. 1995. Defective protein folding as a basis of human disease. Trends in Biochemical Sciences. 20:456-459.

Thomas, P.K. 1999. Overview of Charcot-Marie-Tooth disease type 1A. Ann. NY Acad. Sci. 883:1-5.

Tokunaga, F., C. Brostrom, T. Koide, and P. Arvan. 2000. Endoplasmic reticulum (ER)-associated degradation of misfolded N-linked glycoproteins is suppressed upon inhibition of ER mannosidase I. J. Biol. Chem. 275:40757-40764.

Trombetta, E.S., and A. Helenius. 1999. Glycoprotein reglucosylation and nucleotide sugar utilization in the secretory pathway: identification of a nucleoside diphosphatase in the endoplasmic reticulum. EMBO J. 18:3282-3292.

Trombetta, E.S., and A. Helenius. 2000. Conformational requirements for glycoprotein reglucosylation in the endoplasmic reticulum. J. Cell Biol. 148:1123-1130.

Trombetta, E.S., J.F. Simons, and A. Helenius. 1996. Endoplasmic reticulum glucosidase II is composed of a

catalytic subunit, conserved from yeast to mammals, and a tightly bound noncatalytic HDEL-containing subunit. J. Biol. Chem. 271:27509-27516.

Trombetta, S., M. Bosch, and A. Parodi. 1989. Glucosylation of glycoproteins by mammalian, plant, fungal, and trypanosomatid protozoa microsomal membranes. Biochemistry. 28:8108-16.

Trombetta, S., and A. Parodi. 1992. Purification to apparent homogeneity and partial characterization of rat liver UDP-glucose:glycoprotein glucosyltransferase. J. Biol. Chem. 267:9236-40.

Van Leeuwen, J.E.M., and K.P. Kearse. 1997. Reglucosylation of N-linked glycans is critical for calnexin assembly with T cell receptor (TCR) alpha proteins but not TCRbeta proteins. J. Biol. Chem. 272:4179-4186.

Vashist, S., W. Kim, W.J. Belden, E.D. Spear, C. Barlowe, and D.T.W. Ng. 2001. Distinct retrieval and retention mechanisms are required for the quality control of endoplasmic reticulum protein folding. J. Cell Biol. 155:355-368.

Veijola, J., and R.F. Pettersson. 1999. Transient association of calnexin and calreticulin with newly synthesized G1 and G2 glycoproteins of uukuniemi virus (family Bunyaviridae). J. Virol. 73:6123-6127.

Verpy, E., E. Couture-Tosi, and T. M. 1993. C1 inhibitor mutations which affect intracellular transport and secretion in type I hereditary angioedema. Behring Inst Mitt. 93:120-4.

Vinayagamoorthy, T., and A. Rajakumar. 1996. Stress relief protein modulation by calnexin. Ann. NY Acad. Sci. 793:479-84.

Wada, I., M. Kai, S. Imai, F. Sakane, and H. Kanoh. 1997. Promotion of transferrin folding by cyclic interactions with calnexin and calreticulin. EMBO J. 16:5420-5432.

Weng, S., and R. Spiro. 1993. Demonstration that a kifunensine-resistant alpha-mannosidase with a unique processing action on N-linked oligosaccharides occurs in rat liver endoplasmic reticulum and various cultured cells. J. Biol. Chem. 268:25656-63.

White, A.L., B. Guerra, J. Wang, and R.E. Lanford. 1999. Presecretory degradation of apolipoprotein[a] is mediated by the proteasome pathway. J. Lipid Res. 40:275-286.

Wiertz, E., D. Tortorella, M. Bogyo, J. Yu, W. Mothes, T. Jones, T. Rapoport, and H. Ploegh. 1996. Sec61-mediated transfer of a membrane protein from the endoplasmic reticulum to the proteasome for destruction. Nature. 384:432-8.

Wu, S., C. Lee, C. Liao, R. Dwek, N. Zitzmann, and Y. Lin. 2002. Antiviral effects of an iminosugar derivative on flavivirus infections. J. Virol. 76:3596-604.

Yamamoto, K., R. Fujii, Y. Toyofuku, T. Saito, H. Koseki, V.W. Hsu, and T. Aoe. 2001. The KDEL receptor mediates a retrieval mechanism that contributes to quality control at the endoplasmic reticulum. EMBO J. 20:3082-3091.

Yamashita, Y., K. Shimokata, S. Mizuno, T. Daikoku, T. Tsurumi, and Y. Nishiyama. 1996a. Calnexin acts as a molecular chaperone during the folding of glycoprotein B of human cytomegalovirus. J. Virol. 70:2237-2246.

Yamashita, Y., M. Yamada, T. Daikoku, H. Yamada, A. Tadauchi, T. Tsurumi, and Y. Nishiyama. 1996b. Calnexin associates with the precursors of glycoproteins B, C, and D of herpes simplex virus type 1. Virology. 225:216-22.

Ye, Y., H. Meyer, and T. Rapoport. 2001. The AAA ATPase Cdc48/p97 and its partners transport proteins from the ER into the cytosol. Nature. 414:652-6.

Yool, D., J. Edgar, P. Montague, and S. Malcolm. 2000. The proteolipid protein gene and myelin disorders in man and animal models. Hum. Mol. Genet. 9:987-92.

Yoshida, H., T. Matsui, N. Hosokawa, R.J. Kaufman, K. Nagata, and K. Mori. 2003. A time-dependent phase shift in the mammalian unfolded protein response. Dev. Cell. 4:265-71.

Yoshida, Y., T. Chiba, F. Tokunaga, H. Kawasaki, K. Iwai, T. Suzuki, Y. Ito, K. Matsuoka, M. Yoshida, K. Tanaka, and T. Tai. 2002. E3 ubiquitin ligase that recognizes sugar chains. Nature. 418:438-42.

Zapun, A., N.J. Darby, D.C. Tessier, M. Michalak, J.J.M. Bergeron, and D.Y. Thomas. 1998. Enhanced catalysis of Ribonuclease B folding by the interaction of calnexin or calreticulin with ERp57. J. Biol. Chem. 273:6009-6012.

Zapun, A., C. Jakob, D. Thomas, and J. Bergeron. 1999. Protein folding in a specialized compartment: the endoplasmic reticulum. Structure Fold. Des. 7:R173-82.

Zapun, A., S. Petrescu, P. Rudd, R. Dwek, D. Thomas, and J. Bergeron. 1997. Conformation-independent binding of monoglucosylated ribonuclease B to calnexin. Cell. 88:29-38.

Zuber, C., J.-y. Fan, B. Guhl, A. Parodi, J.H. Fessler, C. Parker, and J. Roth. 2001. Immunolocalization of UDP-glucose:glycoprotein glucosyltransferase indicates involvement of pre-Golgi intermediates in protein quality control. PNAS. 98:10710-10715.

Zuber, C., M.J. Spiro, B. Guhl, R.G. Spiro, and J. Roth. 2000. Golgi apparatus. Immunolocalization of endomannosidase suggests post-endoplasmic reticulum glucose trimming: Implications for quality control. Mol. Biol. Cell. 11:4227-4240.

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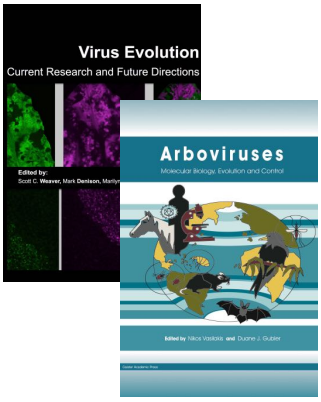

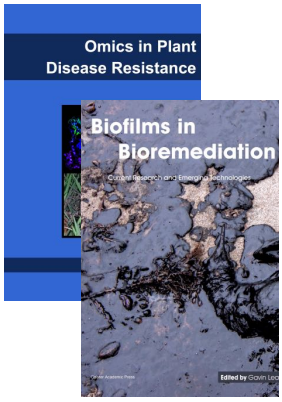

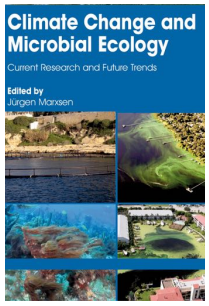

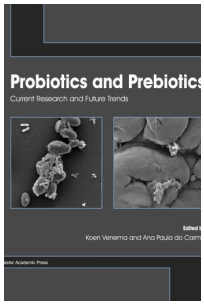

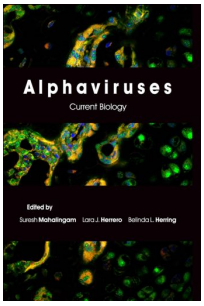

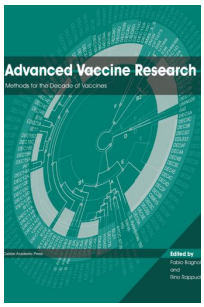

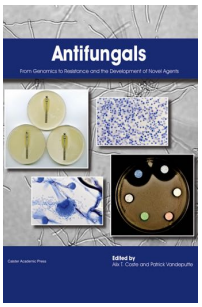

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