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Review

A sweet code for glycoprotein folding

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ABSTRACT

Glycoprotein synthesis is initiated in the endoplasmic reticulum (ER) lumen upon transfer of a glycan ($Glc_3Man_9GlcNAc_2$) from a lipid derivative to Asn residues (*N*-glycosylation). *N*-Glycan-dependent quality control of glycoprotein folding in the ER prevents exit to Golgi of folding intermediates, irreparably misfolded glycoproteins and incompletely assembled multimeric complexes. It also enhances folding efficiency by preventing aggregation and facilitating formation of proper disulfide bonds. The control mechanism essentially involves four components, resident lectin-chaperones (calnexin and calreticulin) that recognize monoglucosylated polymannose protein-linked glycans, lectin-associated oxidoreductase acting on monoglucosylated glycoproteins (ERp57), a glucosyltransferase that creates monoglucosylated epitopes in protein-linked glycans (UGGT) and a glucosidase (GII) that removes the glucose units added by UGGT. This last enzyme is the only mechanism component sensing glycoprotein conformations as it creates monoglucosylated glycans exclusively in not properly folded glycoproteins or in not completely assembled multimeric glycoprotein complexes. Glycoproteins that fail to properly fold are eventually driven to proteasomal degradation in the cytosol following the ER-associated degradation pathway, in which the extent of *N*-glycan demannosylation by ER mannosidases play a relevant role in the identification of irreparably misfolded glycoproteins.
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1. Introduction – the ER as the initial site of protein secretion

Nearly one third of eukaryotic proteins belong to the secretory pathway, representing about 8000 proteins in humans. Most of them are synthetized by ribosomes attached to the endoplasmic reticulum (ER) and enter into the ER through the Sec61 αβγ translocon complex. Alternatively, some proteins may enter post-translationally. This pathway is more frequently employed in yeast [1]. Secretory pathway proteins fold and assemble in the ER before continuing their journey. Topologically equivalent to the cell exterior, the lumen of the ER is a highly crowded environment, with an oxidizing potential and high calcium concentration, which ranges in the order of millimolar. For this reason, secretory pathway proteins face unique challenges in order to fold properly in this potentially hostile environment. The ER molecular chaperones belong to protein families commonly found in other locations, such as HSP70 (BiP in the ER) and HSP90 (GRP94 in the ER), but lacks chaperonine-like proteins. This absence can be partially compensated by GRP94 which, by recognizing advanced folding intermediate, collaborates with BiP in assisting the folding pathway of selected substrates [2]. Concomitantly with their folding, most secretory pathway proteins acquire disulfide bridges and are *N*-glycosylated in the ER. Compared with proteins in other locations, secretory pathway proteins have a higher frequency of disulfide bonds, which stabilize their tertiary structure and oligomer association. A varied group of protein disulfide isomerases (PDIs), unique to the ER, guarantee the fidelity of the oxidation process. Equally important, the presence of *N*-glycans allows the operation of specialized mechanisms that assist the protein folding.

2. *N*-glycosylation

Approximately one quarter of the eukaryotic proteins are *N*-glycosylated at the lateral chain of Asn residues displayed within the consensus sequence Asn-Xxx-Ser/Thr, where Xxx cannot be Pro (in some cases Asn-Xxx-Cys, Asn-Gly or Asn-Xxx-Val sequences can also be used) [3]. This motif, named *N*-glycosylation sequon, is quite common, with a frequency of about 4–10 sequons every 1000 residues [4].

In most organisms the glycan $Glc_3Man_9GlcNAc_2$ (G3M9) (Figs. 1A, B and 2) is initially transferred *en bloc* from a dolichol-pyrophosphate-oligosaccharide, while some protozoans transfer a shorter version. For instance, *Trypanosome cruzi* uses an

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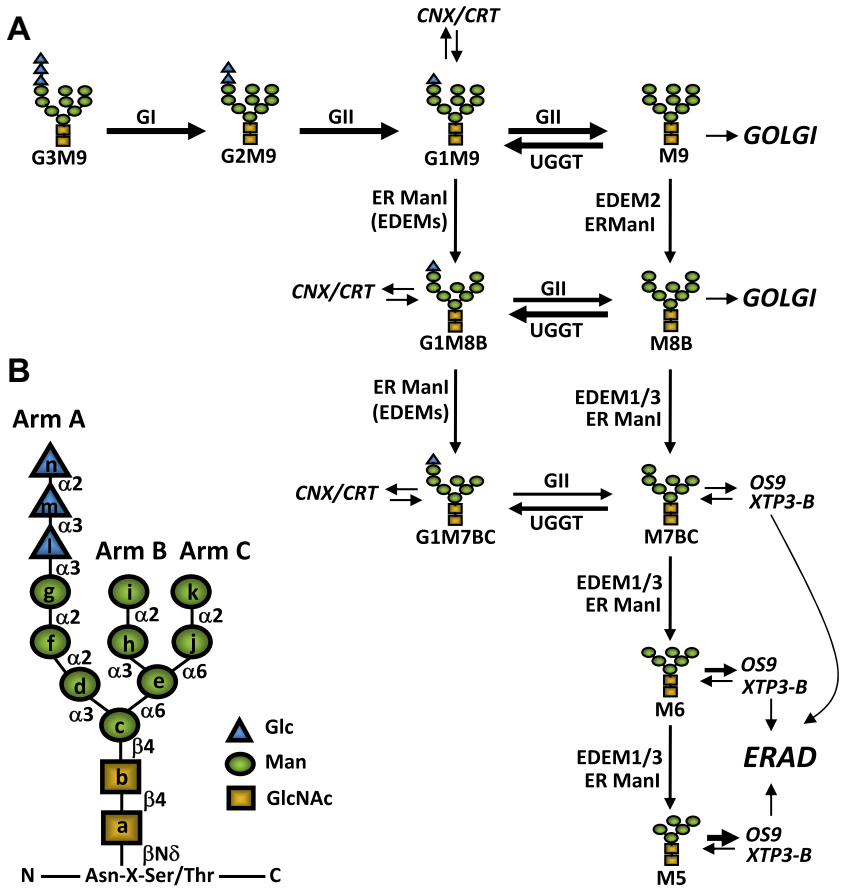

Fig. 1. (A) Processing and recognition of *N*-glycans in the early secretory pathway. (B) Structure of the $Glc_3Man_9GlcNAc_2$ glycan transferred by the oligosaccharyltransferase.

oligosaccharide that lacks glucose residues ($Man_9GlcNAc_2$, M9) [5]. The homogeneity of the *N*-glycan transferred among different species is in sharp contrast with the enormous variability of *N*-glycans displayed by mature glycoproteins at their final destinations. This diversity is acquired through the action of several glycosidases and glycosyltransferases located partially in the ER but mainly in the Golgi apparatus, following a complex and non-linear process. In mature complex glycoproteins the core glycan $Man_3GlcNAc_2$ (M3) is usually the only remnant of the transferred glycan. This observation points to the dual biological functions of *N*-glycans [6]. On one hand, the great variety of glycosidic linkages and monosaccharide units makes *N*-glycans perfectly suited to play a central role in many molecular recognition events at the cell surface. A diverse array of biological processes are modulated or mediated by *N*-glycans, such as differentiation, migration and proliferation. On the other hand, early high mannose *N*-glycans assist to the protein folding process of several glycoproteins. Due to their bulky and hydrophilic nature, *N*-glycans can be considered as covalently attached chemical chaperones. They prevent protein aggregation by hindering hydrophobic aggregation-prone regions, acting as a kind of hydrophilic shield. They can also facilitate the acquisition of secondary structure elements such as turns [7]. In addition, *N*-glycans are used as a "bar code" to display information regarding the folding status and age of glycoproteins. This code is generated and interpreted by several glycosidases, glycosyltransferases and lectins operating in the early secretory pathway. In brief, monoglucosylated *N*-glycans are a signature of glycoproteins displaying immature conformations, while progressive loss of mannose residues marks slowing folding or terminally misfolded proteins, eventually leading them to degradation. These intertwined processes, protein folding quality control (QC) and endoplasmic reticulum associated degradation (ERAD), are discussed in the following sections and are schematically outlined in Figs. 1A and 2).

3. The ER glucosidases

The two outermost glucose residues of the initially transferred glycan G3M9 are rapidly removed by the sequential action of glucosidase I (GI) and glucosidase II (GII), thus generating the monoglucosylated intermediate $Glc_1Man_9GlcNAc_2$ (G1M9). This glycan is recognized by ER resident lectins calreticulin (CRT), which is a soluble protein and its type I integral membrane paralogue calnexin (CNX), that retain the glycoproteins in the ER until GII cleaves the last glucose residue. At this point, properly folded proteins leave the ER toward their final destination. By contrast, those proteins unable to attain a native conformation or incompletely assembled complexes are recognized by the enzyme UDP-glucose:glycoprotein glucosyltransferase (UGGT) that adds the last glucose removed by GII exclusively to glycoproteins not displaying their native conformations, thus re-creating the G1M9 structure. This process allows the re-association of glycoproteins and CRT/CNX. Cycles of deglucosylation by GII and reglucosylation by UGGT continue until the glycoprotein folds properly, that is, when they are no longer recognized by the last enzyme [8]. Alternatively, proteins unable to fold properly are eventually directed to degradation by the ERAD machinery [9].

The α1,2-exoglucosidase GI is a type II membrane protein with a short cytosolic tail that belongs to the glycosylhydrolase 63

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