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Review

Non-lysosomal degradation pathway for *N*-linked glycans and dolichol-linked oligosaccharides

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ABSTRACT

There is growing evidence that asparagine (*N*)-linked glycans play pivotal roles in protein folding and intra- or intercellular trafficking of *N*-glycosylated proteins. During the *N*-glycosylation of proteins, significant amounts of free oligosaccharides (fOSs) and phosphorylated oligosaccharides (POSs) are generated at the endoplasmic reticulum (ER) membrane by unclarified mechanisms. fOSs are also formed in the cytosol by the enzymatic deglycosylation of misfolded glycoproteins destined for proteasomal degradation. This article summarizes the current knowledge of the molecular and regulatory mechanisms underlying the formation of fOSs and POSs in mammalian cells and *Saccharomyces cerevisiae*.

Contents

1. Introduction

N-Glycosylation is one of the most common co- and posttranslational modifications of eukaryotic proteins occurring in the lumen of the endoplasmic reticulum (ER) [1–5]. *N*-Glycans affect the physicochemical (*e.g.*, solubility or thermal stability) and physiological (*e.g.*, bioactivity or intra-/intercellular trafficking) properties of modified proteins [6]. We, former trainees of Dr. Lennarz as post-doctoral researchers, have investigated the mechanism regulating the "birth and death" of *N*-glycans [7–22]. The biosynthetic pathways leading to *N*-glycosylation in mammalian cells or yeast are well clarified [2], while the molecular details of catabolic pathways involved in glycan breakdown are less well understood, especially for processes occurring outside of the lysosome. In this article, we present an overview of the current knowledge of the "non-lysosomal degradation pathway" for *N*-glycans and dolichol-linked oligosaccharides (DLOs), focusing on mammalian cells and the budding yeast, *Saccharomyces cerevisiae*.

2. fOSs formed in the ER

During the translocation of proteins into the ER, the oligosaccharyltransferase (OST) enzyme complex transfers oligosaccharide (OS) moieties from the DLO substrate to the asparagine residue located within the consensus sequence –Asn-Xaa-Ser/Thr– (where

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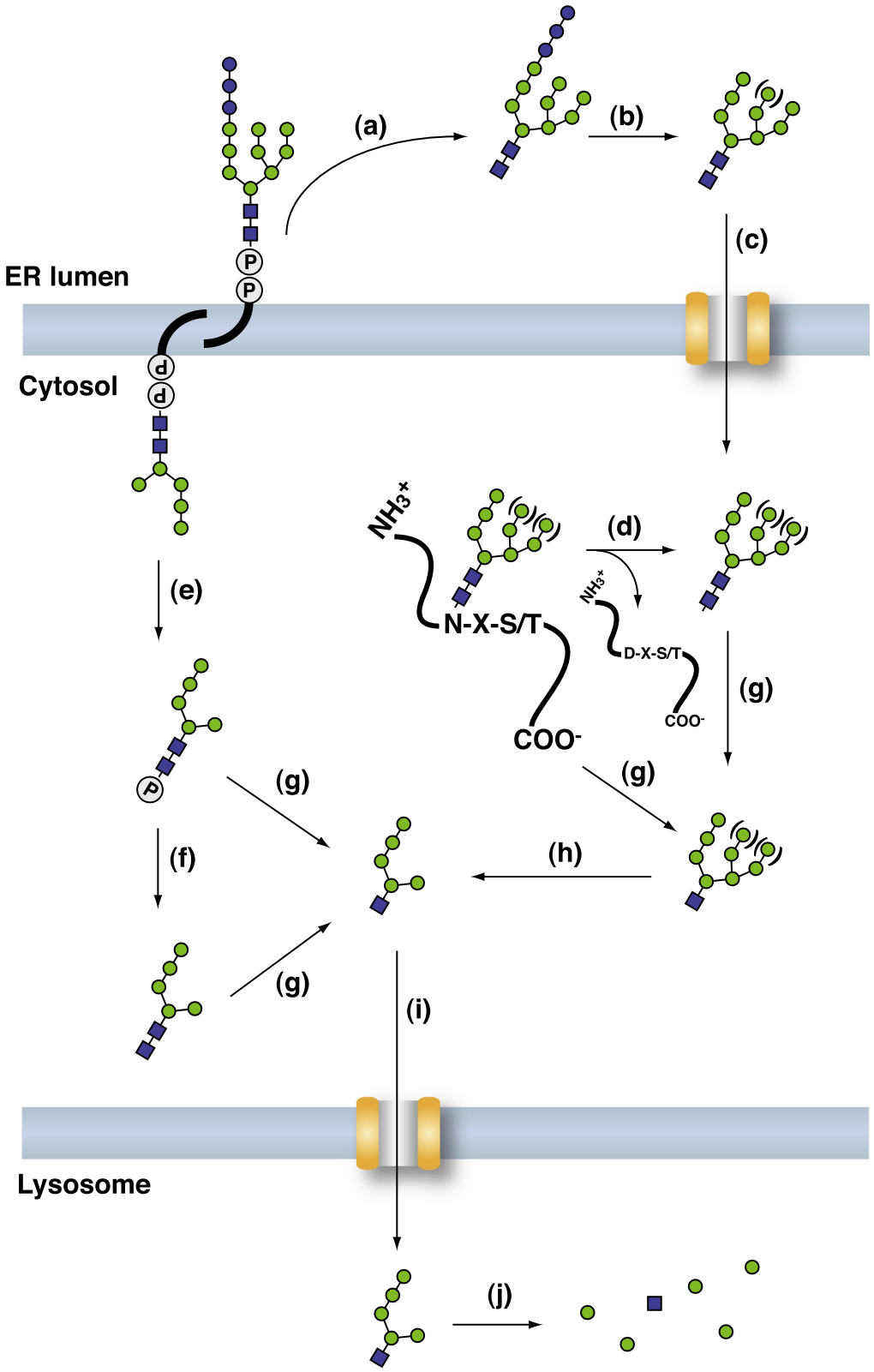

Fig. 1. Current proposed model for the fate of fOSs formed in and outside of the ER in mammalian cells. Gn2-type fOSs are generated in the lumen of the ER by an undefined mechanism (step (a)). After quick deglycosylation by α-glucosidases I/II (and sometimes ER α-mannosidase I) (step (b)), $Man_{8\text{-}9}GlcNAc_2$ is transported into the cytosol by an oligosaccharide transporter in the ER membrane (step (c)). Gn2-type fOSs can also be generated by the action of cytoplasmic PNGase on misfolded glycoproteins (step (d)). Putative pyrophosphatase activity, which has been proposed to be located on the cytosolic side of the ER membrane, releases POSs from the DLOs (step (e)). POSs may be converted to Gn2-type fOSs by the putative POS phosphatase (step (f)). In the cytosol, ENGase acts on Gn2-type fOSs, and possibly on POSs or misfolded glycoproteins, to form Gn1-type glycans (steps (g)). The Gn1-type glycans are susceptible to the action of Man2C1, giving rise to the specific $Man_5GlcNAc$ structures (step (h)). The isomeric structure of Man_5 is identical to that of the last biosynthetic intermediate of pyrophosphoryl dolichol oriented to the cytosolic side of the ER membrane. The $Man_5GlcNAc$ glycan (and possibly more trimmed $Man_{3\text{-}4}GlcNAc$ glycans) may be transported into the lysosomes by an unidentified oligosaccharide transporter (Step (i)). In the lysosome, the incorporated fOSs are hydrolyzed into monomeric sugars by lysosomal glycosidases for reutilization (step (j)). For more details, please see text.

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