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The Role Of The ER Glucosyltransferase In The Quality Control Of Glycoprotein Maturation

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Abstract
N-linked glycans serve as quality control tags in the eukaryotic secretory pathway. The endoplasmic reticulum (ER) protein UDP-glucose: glycoprotein glucosyltransferase 1 (GT1) is the main enzyme that modifies carbohydrate tags based upon the folding state of the maturing

substrate. GT1 adds glucoses to non-glucosylated proteins that fail the quality control test, supporting ER retention through persistent binding to the lectin chaperones calnexin and calreticulin. How GT1 functions in its native environment on a maturing substrate as well as its ability to differentiate between native or aberrant secretory cargo is poorly understood. Additionally, due to inherent difficulties in studying GT1 activity in the cell, identification of endogenous substrates and the necessity of reglucosylation remain unknown. Here, we analyzed the role of GT1 in glycoprotein maturation in the intact mammalian ER. GT1 post-translationally reglucosylates N-linked glycans in slow-folding regions of substrate glycoproteins. Maturation mutants that disrupt oxidation or oligomerization also support regio-specific reglucosylation by GT1. Our studies have also revealed an abundant endogenous substrate of GT1, identified as prosaposin. GT1 is critical for the maturation of endogenous prosaposin. In the absence of GT1, the endogenous protein is mislocalized to large intracellular juxtanuclear aggregates. Together, these results propose that GT1 acts as an ER quality control sensor by post-translationally targeting glycans on slow folding or non-native domains to recruit chaperones specifically to critical unstable regions. GT1 plays a vital role in endogenous protein folding and trafficking, since in its absence misfolded proteins accumulate intracellularly. This investigation provides new insight into the integral role of GT1 in glycoprotein maturation.