N-glycan structures, lectin domains, and glycoprotein's fate in the secretory pathway

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N-glycans transferred to proteins are remodeled in the endoplasmic reticulum (ER) producing structures that determine the fate of the glycoproteins within the secretory pathway. Glucosidase II (GII) is a key player in *N*-glycan processing as it removes the two inner glucose residues from the glycan transferred to proteins during *N*-glycosylation and the glucose residue added back to not yet properly folded proteins during the quality control of glycoprotein folding in the ER. GII is a heterodimer whose alpha subunit bears the catalytic site while its beta subunit enhances deglucosylation activity through its C-terminal Mannose-6-phosphate (M6P) receptor homology (MRH) domain. A family of glycan receptors bearing MRH domains, including CD-MPR & CI-MPR (responsible for delivering acidic hydrolases with M6P signal to lysosomes), *N*-acetylglucosamine-1-phosphotransferase g subunit (responsible of generating the M6P signal), OS-9 (involved in the glycoprotein degradation pathway) and GII beta subunit recognize subtle differences in the *N*-glycan structures. Comparison of their structures showed a similar overall fold and identified conserved residues critical for the structural integrity of the carbohydrate binding pocket. Nonetheless, each one has its unique substrate specificity and its binding defines if the protein will continue in the folding process, will be delivered to lysosomes or will be degraded in proteasomes. In the present work, we show the effects on GII activity of swapping its own GII beta MRH domain for those MRH domains present in other lectins of the secretory pathway

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