Knowing and controlling the glycoprotein folding cycle by chemical synthesis

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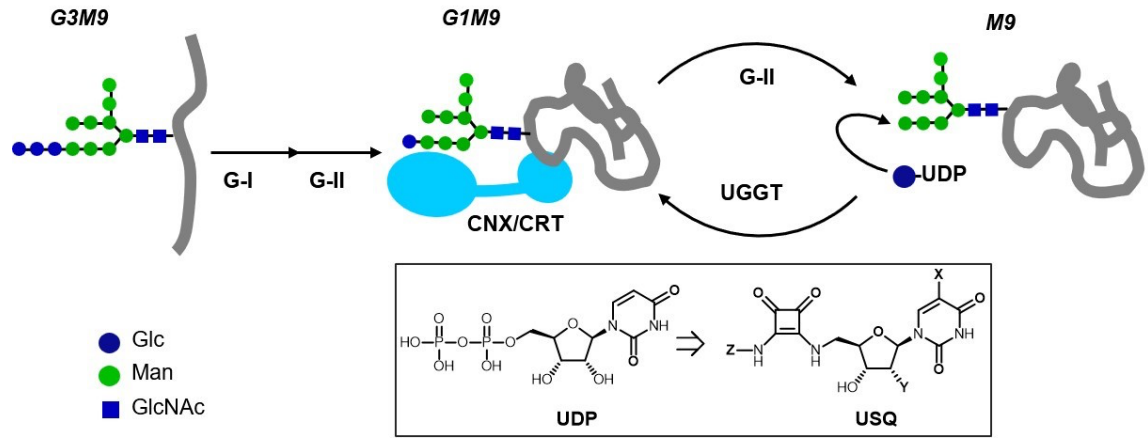
In eukaryotic cells, protein N-glycosylation occurs in the lumen of the ER, introducing the common precursor consisting of three glucose (Glc), nine mannose (Man), and two N-acetylglucosamine (GlcNAc) residues ($Glc_3Man_9GlcNAc_2$; G3M9). Subsequent digestion by glucosidase-I (G-I) and -II (G-II) sequentially removes terminal and penultimate Glc residues to produce the monoglucosylated glycoform (G1M9) which enters the N-glycosylation dependent folding cycle, consisting of lectin chaperones calnexin (CNX) or calreticulin (CRT), G-II, and UGGT.

In this cycle, glycoproteins captured by CNX or CRT are digested by G-II, removing the innermost Glc residue to generate the non-glucosylated glycoform ($Man_9GlcNAc_2$; M9). On the other hand, the glucosyltransferase UGGT functions as a folding sensor. When glycoproteins have failed to achieve correct folding, they are captured by UGGT which regenerates the G1M9 by glucosylation of the M9 using UDP-Glc as the donor substrate, thus allowing client glycoproteins to repeatedly interact with CNX/CRT. Using chemically synthesized glycans[1] and glycoproteins,[2]we have carried out systematic studies to clarify the properties of the components of the CNX/CRT cycle.[3] Molecules that perturb their activities would be valuable for knowing their roles. To that end, our recent effort aimed to develop UGGT inhibitors through structural modification of the enzyme's natural ligand UDP. The UDP analogs (USQ) having substituted squaryl group were shown to exhibit significant activity to inhibit UGGT.[4]



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[4] J. Abe, et al. (2023), submitted.