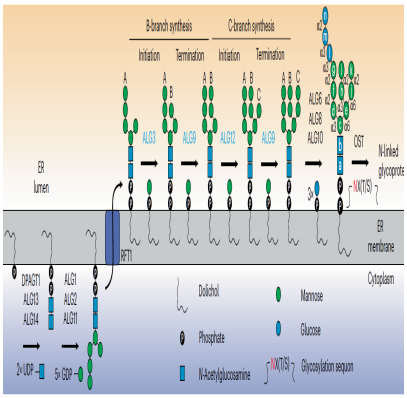

Revealing the Assembly logic of the N-glycan oligomannose core construction

Description

Asparagine-linked glycans are essential for the maturation and function of most eukaryotic secretory proteins. The biosynthesis and transfer of the dolichylpyrophosphate-anchored GlcNAc2Man9Glc3 glycan is a highly conserved process that occurs in the endoplasmic reticulum (ER) membrane and involves over a dozen membrane proteins, whose dysfunction is linked to congenital disorders of glycosylation (CDGs). Three membrane-integral mannosyltransferases, ALG3, ALG9, and ALG12, mediate four consecutive mannosylation reactions that convert GlcNAc2Man5 to GlcNAc2Man9.

Using chemoenzymatically synthesized lipid-linked glycan donor and acceptor analogs, the authors recapitulated this biosynthetic pathway in vitro. High-resolution cryo-electron microscopy structures of pseudo-Michaelis complexes at each step revealed how the branched glycan is accurately synthesized and how unwanted side products are avoided. Molecular dynamics simulations and mutagenesis studies uncovered a subtle yet precise mechanism that selects the dolichylphosphomannose donor substrate over dolichylphosphoglucose, which is also present in the ER membrane. The results also provide mechanistic explanations for enzyme dysfunction in CDGs and offer opportunities for N-glycan engineering.

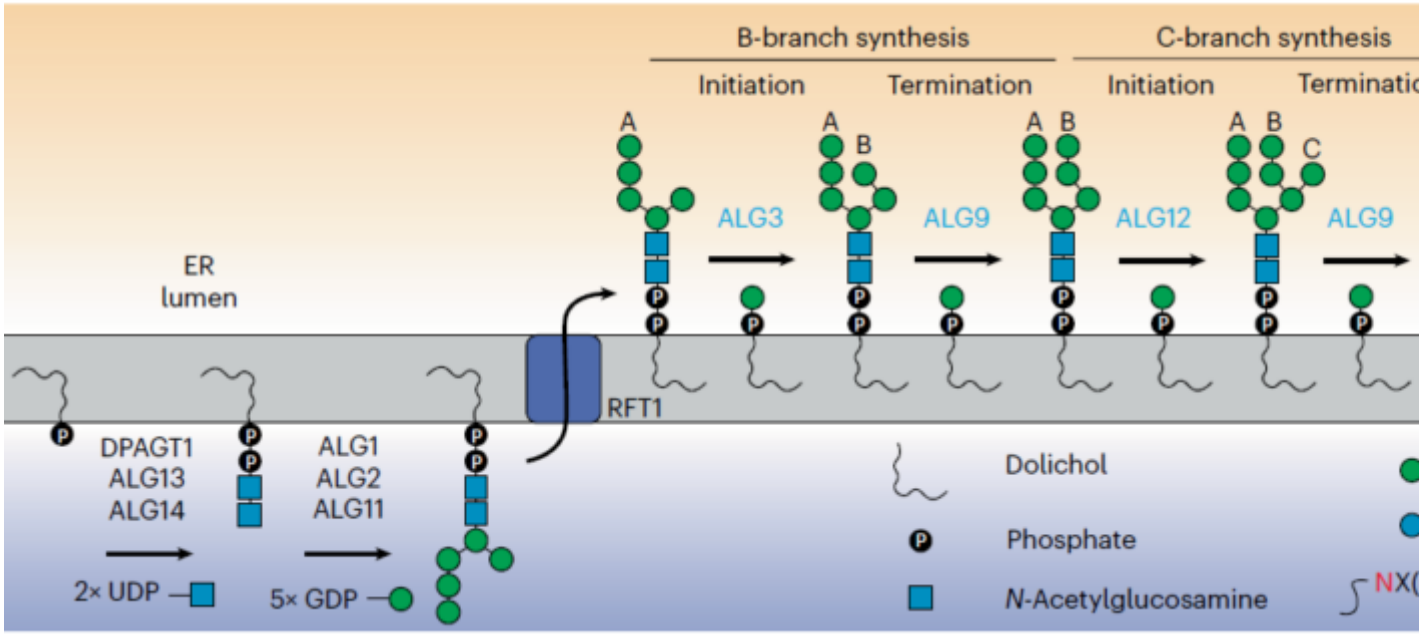

Fig. 1 | Functional reconstitution of oligomannose synthesis. a, Schematic of *N*-glycan synthesis in the human ER

Category

1. News