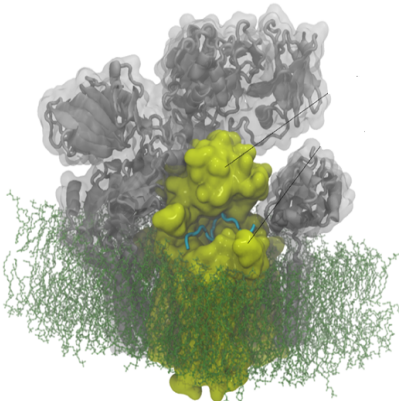
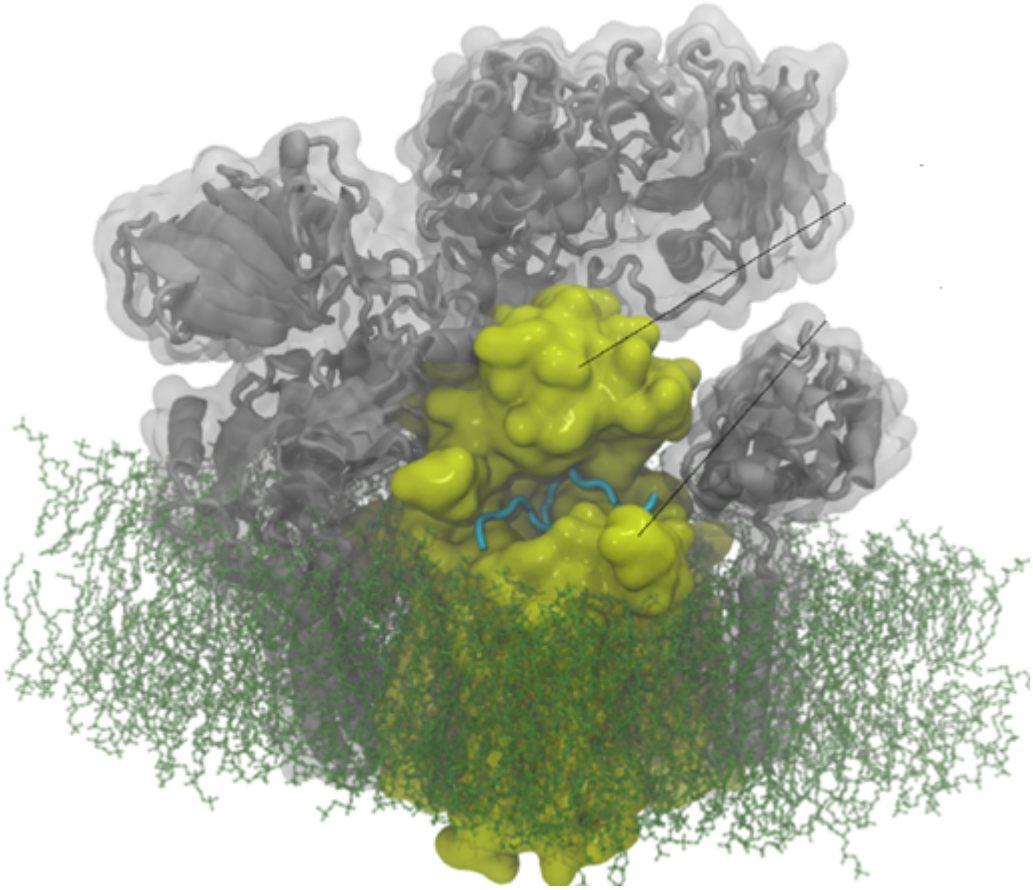


Regulation of N-glycosylation efficiency by eukaryotic oligosaccharyltransferase

Description

Oligosaccharyltransferase (OST) catalyses the key step of *N*-glycosylation, transferring immature *N*-glycans to select Asn residues in nascent proteins in the endoplasmic reticulum (ER). Asn are more likely to be glycosylated in the context of a â??glycosylation sequonâ?•, N-x-S/T (xâ? P), but not every sequon is glycosylated. Tight positive and negative regulation of site-specific *N*-glycosylation across the glycoproteome is essential because some Asn require glycosylation for productive protein folding or function, while others must remain unglycosylated. Despite its importance, the underlying bases for this regulation are ill-defined. The authors characterise the molecular determinants regulating OST catalytic efficiency.They identify preferred substrates of OST and show that the local sequence determines glycosylation efficiency by fine-tuning binding to an extended groove in OST along an eight residue stretch centered at the Asn acceptor. Tight control of OST activity is achieved through a â??switchâ??, set â??ONâ?? when a peptide binds with high complementarity to the groove, triggering release of the assisting base Glu350 for catalysis. Based on analysis of buried sequons, the authors identify sequence characteristics associated with inherently non-preferred acceptor substrates for OST, and show these have a high propensity for local secondary structure incompatible with the optimal conformation of a peptide bound to OST. Finally, validation of these mechanisms was performed by examining the determinants of efficient glycosylation at a variably glycosylated Asn in a set of human Fabs. These mechanistic and functional insights show how local protein sequence controls glycosylation occupancy with immediate implications in secretory protein function and evolution, pathogen immunity and epistasis, and in engineering protein sequences for the desired degree of site-specific glycosylation.



Category

1. News