Translocation:

* Targeting signals to the endoplasmic reticulum consist of two categories: signal recognition particle (SRP)-dependent, co-translational targeting (reviewed in [[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B2-ijms-22-06284)]) and SRP-independent, post-translational targeting. SRP-independent targeting in mammals includes small secretory proteins [[20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B20-ijms-22-06284),[21](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B21-ijms-22-06284),[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B22-ijms-22-06284)], tail-anchored proteins [[23](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B23-ijms-22-06284),[24](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B24-ijms-22-06284)], and other proteins not efficiently recognized by SRP [[25](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B25-ijms-22-06284),[26](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230904/#B26-ijms-22-06284)]. [[10.3390/ijms22126284](https://doi.org/10.3390%2Fijms22126284)]

ERAD

* Recognition
  + The HRD1 E3 ubiquitin ligase, which is embedded in the ER membrane, is involved in translocating ERAD substrates across the ER membrane and catalyzing substrate ubiquitination via its cytosolic RING finger domain[10](https://www.nature.com/articles/srep20261#ref-CR10). SEL1L, the mammalian homolog of Hrd3p, associates with HRD1, mediates HRD1 interactions with the ER luminal lectin OS9 and recognizes substrates to be degraded[6](https://www.nature.com/articles/srep20261#ref-CR6),[11](https://www.nature.com/articles/srep20261#ref-CR11),[12](https://www.nature.com/articles/srep20261#ref-CR12),[13](https://www.nature.com/articles/srep20261#ref-CR13),[14](https://www.nature.com/articles/srep20261#ref-CR14),[15](https://www.nature.com/articles/srep20261#ref-CR15). [10.1038/srep20261]

Golgi Processing

* N-glycan processing in the Golgi
  + *N*-linked oligosaccharides are processed within the [Golgi apparatus](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3102/) in an ordered sequence of reactions ([Figure 9.24](https://www.ncbi.nlm.nih.gov/books/NBK9838/figure/A1503/?report=objectonly)). The first modification of [proteins](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3297/) destined for secretion or for the [plasma membrane](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3256/) is the removal of three additional mannose residues. This is followed by the sequential addition of an *N*-acetylglucosamine, the removal of two more mannoses, and the addition of a fucose and two more *N*-acetylglucosamines. Finally, three galactose and three sialic acid residues are added. As noted in Chapter 7, different glycoproteins are modified to different extents during their passage through the Golgi, depending on both the structure of the protein and on the amount of processing [enzymes](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3042/) that are present within the Golgi complexes of different types of cells. Consequently, proteins can emerge from the Golgi with a variety of different *N*-linked oligosaccharides. [https://www.ncbi.nlm.nih.gov/books/NBK9838/#:~:text=Protein%20processing%20within%20the%20Golgi,to%20proteins%20in%20the%20ER.]
  + About half of all human proteins are glycoproteins, and most of them are *N*-glycosylated ([Apweiler et al., 1999](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full" \l "B2)). *N*-glycans are synthesized as a lipid-linked oligosaccharide (LLO) precursor. When a new protein is synthesized, the 14-sugar chain GlcNAc2Man9Gluc3 of the LLO is transferred by the oligosaccharyltransferase (OST) to the amide group of the asparagine residue in the Asn-X-Ser/Thr motif, where X is any amino acid except proline ([Kelleher and Gilmore, 2006](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B40)). Before the glycoprotein leaves the ER, all three glucose residues and one particular mannose residue are removed. The resulting *N*-glycans are referred to as the high-mannose subtype and further trimmed in the *cis-*Golgi. Subsequently, the decoration of GlcNAc on mannose yields sugar branches in the *medial-*Golgi. Attachment of galactose, sialic acid, and fucose in the *trans-*Golgi generates complex *N*-glycans ([Stanley et al., 2009](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B78)). One single protein could possess multiple sugar chains added to different amino acids. Notably, sugar chains could be processed diversely, resulting in hybrid *N*-glycans which harbor both high-mannose and complex characteristics ([Ungar, 2009](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B85)). Therefore, the precise *N*-glycan modifications are generated by the accurate removal and addition of sugars in the Golgi, depending on the sequential distribution of the glycosylation enzymes in different cisternae. The same holds true for the nucleotide sugar transporters, which need to be precisely present in the right cisternae ([Hirschberg et al., 1998](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B33)). [[10.3389/fcell.2021.665289](https://doi.org/10.3389/fcell.2021.665289)]
  + Branching
    - The Golgi branching enzymes N-acetylglucosaminyltransferases I, II, IV, V and avian VI (encoded by Mgat1, Mgat2, Mgat4a/b/c Mgat5 and Mgat6), each catalyze the addition of N-acetylglucosamine (GlcNAc) in N-glycans. [[10.1093/glycob/cwu105](https://doi.org/10.1093/glycob/cwu105)]
* O-linked glycosylation
  + Proteins can also be modified by the addition of carbohydrates to the side chains of acceptor serine and threonine residues within specific sequences of amino acids (*O*-linked [glycosylation](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3099/)) (see [Figure 7.28](https://www.ncbi.nlm.nih.gov/books/n/cooper/A1199/figure/A1216/?report=objectonly)). These modifications take place in the [Golgi apparatus](https://www.ncbi.nlm.nih.gov/books/n/cooper/A2886/def-item/A3102/) by the sequential addition of single sugar residues. The serine or threonine is usually linked directly to *N*-acetylgalactosamine, to which other sugars can then be added. In some cases, these sugars are further modified by the addition of sulfate groups. [https://www.ncbi.nlm.nih.gov/books/NBK9838/#:~:text=Protein%20processing%20within%20the%20Golgi,to%20proteins%20in%20the%20ER.]
  + Unlike the ER origination of *N*-glycosylation, *O*-glycosylation is more diversified and predominantly processed in the Golgi. There are two main types of *O*-glycans in mammalian cells: the matrix glycosaminoglycan (GAG) chains on proteoglycans and the most common mucin-type glycans ([Brockhausen et al., 2009](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full" \l "B15)). The repeating disaccharides of unbranched GAG chains are attached to the serine residues on the core proteins of proteoglycans through a common tetrasaccharide linker (xylose–Gal–Gal–glucuronic acid). The disaccharide units contain either *N*-acetylgalactosamine (GalNAc) or GlcNAc, and a uronic acid, which are extended in the earlier Golgi. The frequent sulfation modification on the disaccharide then occurs in the *trans*-Golgi ([Stanley, 2011](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B77)). Mucin-type *O*-glycosylation initiates with the attachment of a GalNAc onto the Ser/Thr residues in a glycoprotein to form GalNAcα1-Ser/Thr, which is also called the tumor-associated Tn antigen ([Ju et al., 2014](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B39)). A family of enzymes known as polypeptide GalNAc-transferases (ppGalNAcTs) catalyzes this reaction. The Tn antigen is usually a precursor and followed by the addition of galactose, GlcNAc, or GalNAc to form core *O*-glycan structures. The critical step is to transfer galactose by the enzyme termed T-synthase (Core 1 β3-galactosyltransferase, C1GalT1) to form the common core 1 *O*-glycan (or the T antigen). The T antigen can be further processed into core 2 by core 2 GlcNAc transferases (C2GnTs) to generate GlcNAcβ1–6(Galβ1–3) GalNAcα1-Ser/Thr. The core 1 and/or core 2 *O*-glycans are ubiquitously expressed in humans. Although *O*-glycan structures are generally shorter than *N*-glycans, core 1–4 structures could be further extended to generate diverse glycan chains, such as polyLacNAc, Lewis antigens, and different blood group antigens ([Kudelka et al., 2015](https://www.frontiersin.org/articles/10.3389/fcell.2021.665289/full#B45)). [[10.3389/fcell.2021.665289](https://doi.org/10.3389/fcell.2021.665289)]