Lost in Translation — What Happens to Proteins After Expression?

The Cytosol

- All translation begins at the ribosomes in the cytosol

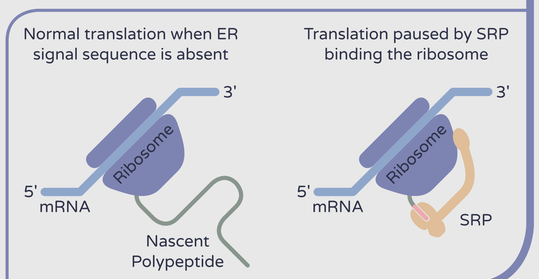
⇅ If a hydrophobic, N-terminal ER signal sequence emerges from the ribosome, a Signal Recognition Particle (SRP) binds to it and pauses translation

⇅ The SRP guides the complex to an SRP Receptor (SR) on the ER membrane where it undergoes co-translational translocation and is released into the ER lumen[1]

N-terminal Acetylation is a common, co-translational modification present in 80-90% of human proteins. Catalysed by Nt-acetyltransferases (NATs). The functional significance of this modification remains unclear[3]

Ubiquitination is the addition of a small protein, ubiquitin to either a lysine residue or the N-terminus of a protein. If a chain of ubiquitin (polyubiquitin) is formed, then this marks the protein for degradation by the 26S proteasome[1,4,5]

Phosphorylation is a very common modification in which kinases add a phosphate group or phosphatases remove one. This can change the conformation of the protein and allows for the energy of ATP to be harnessed[5,6]



An Introduction to Protein Processing

- More often than not, discussions about protein production end at the ribosome; however, taking a deeper look at how proteins are modified and sorted after translation has given birth to entire fields of study (like glycobiology and proteomics).[1]
- The post-translational modification of proteins allows for substantial biological complexity and nuance that cannot be accounted for by DNA alone. Humans, for example, are estimated to have 23,000-40,000 genes, but express upwards of 90,000 unique proteins.[2]
- Finally, countless aspects of biological life depend, directly or indirectly, on carefully regulated protein localisation. Homeostasis is all about maintaining gradients, multicellular life hinges on protein secretion, et cetera.

The Endoplasmic Reticulum (ER)

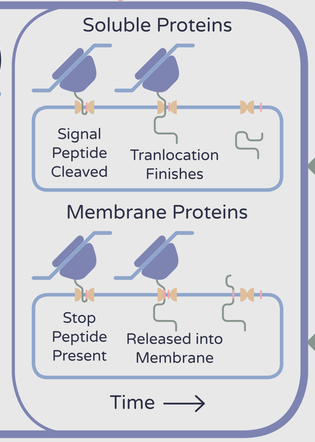
- All proteins that are to be secreted or that end up in the endomembrane system start in the ER[1,8]

⇅ Correctly folded proteins are difficult to translocate, so the ER exports proteins in COPII-coated vesicles[1]

Disulphide Bonding is catalysed by protein disulfide isomerase (PDI) in the ER and is vital to the folding of many proteins[9]

N-linked Glycosylation links oligosaccharides to proteins as they are translocated. The trimming of sugars controls protein release from the ER, ensuring they are properly folded first[1]

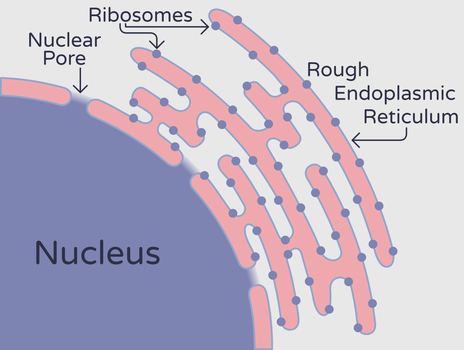
Membrane Embedding is the result of partial translocation. A hydrophobic α-helix can anchor a protein into the bilayer or a GPI anchor can be bonded to the protein[1,10]

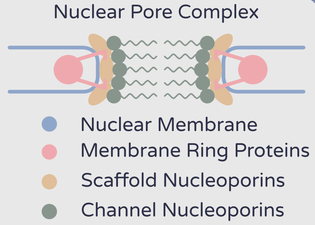


The Nucleus

- Transport mediated by massive nuclear pore complexes (NPCs) composed of 500-1000 proteins[1,7]

⇅ NPCs allow for the free diffusion of small ions but selectively export and import macromolecules like mRNA and proteins[1]





Lysine Acetylation, unlike N-terminal acetylation, is reversible and can be used to regulate protein activity. The acetylation of histones has epigenetic consequences[3,5]

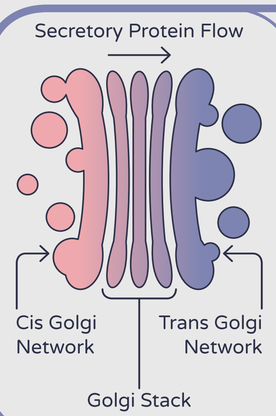
Plastids

Lysosomes

Mitochondria

Plasma Membrane

Peroxisomes



The Golgi Apparatus

- Unlike the ER, all resident proteins of the Golgi are membrane bound

⇅ Vesicles from the ER fuse with the cis Golgi network, pick up modifications as they pass through the stack, then are exported from the trans Golgi network[1]

O-linked Glycosylation tends to attach much larger sugars than N-linked. The Golgi forms the proteoglycans of the ECM and mucus[1]

Proteolysis can activate many zymogens (inactive enzyme precursors) by cutting parts of the peptide chain. Insulin, for example, requires two cuts to become active[11]

Infographic Key

- Gated (Pore) Transport
- Protein Translocation
- Vesicular Transport
- General Information
- ⇅ Sorting / Localisation Step
- **Protein Modification Step**

References

[1] B. Alberts, Molecular biology of the cell, Sixth edition. New York, NY: Garland Science, Taylor and Francis Group, 2015. **[2]** P. M. Harrison, A. Kumar, N. Lang, M. Snyder, and M. Gerstein, "A question of size: the eukaryotic proteome and the problems in defining it," Nucleic Acids Res., vol. 30, no. 5, pp. 1083–1090, Mar. 2002. **[3]** A. Drazic, L. M. Myklebust, R. Ree, and T. Arnesen, "The world of protein acetylation," Biochim. Biophys. Acta BBA - Proteins Proteomics, vol. 1864, no. 10, pp. 1372–1401, Oct. 2016. **[4]** J. M. Lingbeck, J. S. Trausch-Azar, A. Ciechanover, and A. L. Schwartz, "Determinants of Nuclear and Cytoplasmic Ubiquitin-mediated Degradation of MyoD," J. Biol. Chem., vol. 278, no. 3, pp. 1817–1823, Jan. 2003. **[5]** P. Jenö, "Function and Analysis of Post-translational Protein Modifications." **[6]** khanacademymedicine, Protein modifications | Biomolecules | MCAT | Khan Academy. **[7]** G. Kabachinski and T. U. Schwartz, "The nuclear pore complex – structure and function at a glance," J Cell Sci, vol. 128, no. 3, pp. 423–429, Feb. 2015. **[8]** D. S. Schwarz and M. D. Blower, "The endoplasmic reticulum: structure, function and response to cellular signaling," Cell. Mol. Life Sci., vol. 73, pp. 79–94, 2016. **[9]** M. J. Feige and L. M. Hendershot, "Disulfide bonds in ER protein folding and homeostasis," Curr. Opin. Cell Biol., vol. 23, no. 2, pp. 167–175, Apr. 2011. **[10]** T. Kinoshita, "Glycosylphosphatidylinositol (GPI) Anchors: Biochemistry and Cell Biology: Introduction to a Thematic Review Series," J. Lipid Res., vol. 57, no. 1, pp. 4–5, Jan. 2016. **[11]** G. Mayer et al., "The Regulated Cell Surface Zymogen Activation of the Proprotein Convertase PC5A Directs the Processing of Its Secretory Substrates," J. Biol. Chem., vol. 283, no. 4, pp. 2373–2384, Jan. 2008.