A Brief Summary of Protein Targeting in Eukaryotes

Or a brief description of how certain eukaryotic proteins are targeted to the plasma membrane, extracellular matrix or cell wall, ER, vacuole, Golgi, chloroplast, mitochondrion, nucleus and cytoplasm. Note the special features (and sequences) associated with proteins that allow them to reach their proper cellular destinations.

Proteins are produced on ribosomes and can be divided into two general groups based upon whether or not a signal peptide sequence is encoded at their amino terminus. Proteins without a signal peptide are translated on "free" ribosomes and may remain in the cytosol or be transported to the nucleus, mitochondria or chloroplasts. Proteins specifying an N-terminal signal peptide complete translation on ER-attached ribosomes (or "bound" ribosomes) and will either stay in the ER, the Golgi, vacuoles, or be secreted to the plasma membrane, cell wall or extracellular matrix.

For proteins without a signal peptide:

If a protein does not have any sorting sequence, it stays in the cytosol. This is the default pathway for proteins without a signal peptide and without any further targeting information.

For targeting to the nucleus, the proteins have nuclear localization signals around 6 to 20 amino acids long which are rich in basic amino acids (Lys, Arg). The short sequences share little homology among nuclear-localized proteins and can be present anywhere in the protein. These nuclear localization signals are not cleaved from these nuclear proteins.

For targeting to mitochondria, proteins have an N-terminal presequence, which is composed of alternating charged and hydrophobic amino acid residues. These amino acids form an amphipathic helix that facilitates protein translocation across mitochondrial membranes and targets the protein to the mitochondrial matrix. In many cases, an additional piece of sequence is necessary for proper subcompartment localization. For example, mitochondrial proteins located in the intermembrane space have an intermembrane-space-targeting sequence immediately following the matrix-targeting sequence. Outer membrane proteins, besides the N-terminal presequence, also have another sequence that stops transfer and localizes the proteins in the outer membrane. Except for outer membrane proteins, the presequence will be cleaved from the mature proteins.

For targeting to the choloroplast, proteins contain sequences, called transit peptides, which contain 40-50 amino acids. Similar to mitochondrial import presequences, transit peptides are also found at the N terminus. After translocation into the stroma, the transit peptide is enzymatically removed. Like mitochondria, chloroplasts are also composed of multiple subcompartments. If a protein is destined for the thylakoid lumen, it will contain an additional targeting sequence, called a luminal targeting sequence, after the N-terminal transit peptide to allow for correct protein sorting.

Mitochondrial and chloroplast proteins have to be unfolded first and then imported with the

help of chaperones and several membrane-bound proteins. The transport process also requires energy.

For proteins with a signal peptide:

Many proteins, including almost all secreted, ER and Golgi proteins, have N-terminal signal peptides which direct their translocation to the ER lumen during their translation. Actually, it is after translocation that translation is resumed and completed. These signal peptides contain around 16 to 30 amino acids, including at least one positively charged residue, followed by 6 to 12 hydrophobic residues. Signal peptides will be removed from the mature proteins in the ER lumen. Generally, signal peptides from one organism can act on proteins from other organisms.

Proteins will undergo posttranslational modifications, such as hydroxylation, disulfide bond formation, oligomerization and N-glycosylation in the ER. The default pathway for proteins with signal peptides and with no additional targeting information is to proceed through the ER, Golgi, and plasma membrane where they are then secreted into the cell wall (for plants) or extracellular matrix (for animals).

For targeting to the ER, proteins contain a C-terminal KDEL (Lys-Asp-Glu-Leu) sequence which identifies their ER destiny. So even after they move from the ER to the Golgi, they will be transported back to the ER by COPI vesicles from the Golgi.

For targeting to the lysosome, proteins move from the ER to the Golgi where modifications, such as glycosylation and phosphorylation occur. Such modifications, particularly mannose-6-phosphate, serve to target a protein to the lysosome.

Relatively less is known about some proteins localized to the Golgi. All known Golgi enzymes are inserted into the rough ER membrane and are moved by transport vesicles to the Golgi. Their structures are similar: a short N-terminal domain that faces the cytosol, a single transmembrane α helix and a large C-terminal domain that faces the Golgi matrix. The transmembrane helices among Golgi proteins do not share appreciable sequence similarity, but their presence is both necessary and sufficient to cause them to remain in the Golgi. One popular hypothesis argues that these proteins bind together in the phospholipid biolayer, preventing their diffusion to the plasma membrane.

For targeting to the plasma membrane, proteins have additional sequences (e.g., membrane spanning regions, stop transfer sequences, GPI anchors, etc.) which allow them to attach initially to the ER membrane. As membrane material “flows” from the ER to the Golgi and finally to the plasma membrane, these proteins remain associated with the membrane and now appear on the plasma membrane surface.