8.11: Regulating protein localization

The synthesis of proteins occurs in the cytoplasm, where mature ribosomes are located. Generally, if no information is added, a newly synthesized polypeptide will remain in the cytoplasm. Yet even in the structurally simplest of cells, those of the bacteria and archaea, there is more than one place that a protein may need to be to function correctly: it can remain in the cytoplasm, it can be inserted into the plasma membrane or it may be secreted from the cell. Both membrane and secreted polypeptides must be inserted into, or pass through, the plasma membrane.

Polypeptides destined for the membrane or for secretion are generally marked by a specific tag, known as a signal sequence. The signal sequence consists of a stretch of hydrophobic amino acids, often located at the N-terminus of the polypeptide. As the signal sequence emerges from the ribosomal tunnel it interacts with a signal recognition particle (SRP) - a complex of polypeptides and a structural RNA. The binding of SRP to the signal sequence causes translation to pause. SRP acts as a chaperone for a subset of membrane proteins. The nascent mRNA/ribosome/nascent polypeptide/SRP complex will find (by diffusion), and attach to, a ribosome/SRP receptor complex on the cytoplasmic surface of the plasma membrane (in bacteria and archaea) or a cytoplasmic facing membrane (in eukaryotes). This ribosome/SRP receptor is associated with a polypeptide pore. When the ribosome/SRP complex docks with the receptor, translation resumes and the nascent polypeptide passes through the protein pore and so enters into or passes through the membrane. As the polypeptide emerges on the external, non-cytoplasmic face of the membrane, the signal sequence is generally removed by an enzyme, signal sequence peptidase. If the polypeptide is a membrane protein, it will fold and remain within the membrane. If it is a secreted polypeptide, it will be released into the periplasmic space, that is the region topologically outside of the cytoplasm (either within a vesicle or other side of the plasma membrane. Other mechanisms can lead to the release of the protein from the cell.

Because eukaryotic cells are structurally and topologically more complex than bacterial and archaeal cells there are more places for a newly synthesized protein to end up. While we will not discuss the details of those processes, one rule of thumb is worth keeping in mind. Generally, in the absence of added information, a newly synthesized polypeptide will
end up in the cytoplasm. As in bacteria and archaea, a eukaryotic polypeptides destined for secretion or insertion into the cell's plasma membrane or internal membrane systems (that is the endoplasmic reticulum and Golgi apparatus) are directed to their final location by a signal sequence/SRP system. Proteins that must function in the nucleus generally get there because they have a nuclear localization sequence, other proteins are actively excluded from the nucleus using a nuclear exclusion sequence (see above). Likewise, other localization signals and receptors are used to direct proteins to other intracellular compartments, including mitochondria and chloroplasts. While details of these targeting systems are beyond the scope of this course, you can assume that each specific targeting event requires signals, receptors, and various mechanisms that drive what are often thermodynamically unfavorable reactions.

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