



Protein Folding and Quality Control in Cells: From Molecular Chaperones to Disease

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DESCRIPTION

Proteins are the building blocks of life, playing important role in every biological process. For proteins to function correctly, they must fold into precise three-dimensional shapes. Proper protein folding is critical because a protein's shape determines its ability to interact with other molecules and perform its biological function. The process of protein folding however is complex and error-prone, which is why cells have developed robust quality control systems to ensure that proteins fold properly and to manage misfolded proteins. One of the most essential components of this system is a group of proteins known as molecular chaperones, which assist in the proper folding of other proteins. Failure in these quality control systems can lead to severe diseases, maintaining the essential balance between protein folding and cellular health is essential.

Protein folding is a highly organized process that transforms a linear chain of amino acids, the primary structure of a protein, into a three-dimensional shape, known as its native conformation. This conformation is essential for the protein to perform its biological function. The folding process is guided by the chemical properties of the amino acids, which interact with each other to form various structures such as alpha helices and beta sheets. These structures, known as the secondary structure, fold further into more complex arrangements, forming the tertiary structure. For some proteins, multiple polypeptide chains (subunits) come together to form a quaternary structure.

Despite its precision, protein folding can sometimes go wrong due to mutations in the protein's sequence, environmental stresses such as heat or oxidative conditions or errors during synthesis. Misfolded proteins can become dysfunctional, potentially aggregating into insoluble clumps that can be toxic to cells. As a result, cells have evolved intricate quality control systems to ensure that proteins fold correctly and misfolded proteins are managed appropriately. Molecular chaperones are a

class of proteins that play a pivotal role in assisting other proteins to fold correctly. They do not determine the final structure of the protein but provide an environment where folding can occur safely and correctly. Chaperones act at several stages of a protein's life cycle from synthesis on the ribosome to degradation if the protein cannot fold properly.

One of the most well-known families of molecular chaperones is the Heat Shock Proteins (HSPs), named for their increased expression in response to heat stress, which can cause proteins to misfold. Chaperones also participate in protein refolding if the protein becomes misfolded. For example, if a protein loses its structure due to stress, chaperones can recognize the misfolded protein and help it return to its correct shape. When refolding is not possible, chaperones guide the protein to degradation pathways, ensuring that defective proteins do not accumulate and disrupt cellular function. The process of ensuring proteins are correctly folded and functional is known as proteostasis (protein homeostasis). Proteostasis is maintained by a network of quality control systems that monitor proteins from synthesis to degradation. The Ubiquitin-Proteasome System (UPS) and autophagy are two key pathways that remove misfolded or damaged proteins from cells. In the Ubiquitin-Proteasome System, misfolded proteins are tagged with ubiquitin, a small protein that signals the proteasome to degrade the tagged protein into smaller peptides. This system is highly selective, ensuring that only defective proteins are targeted for degradation while functional proteins are preserved. Autophagy, on the other hand, is a process where larger protein aggregates or damaged organelles are enclosed in vesicles and transported to the lysosome for degradation. When protein folding or quality control mechanisms fail, it can lead to a variety of diseases known as protein misfolding disorders. These disorders are characterized by the accumulation of misfolded or aggregated proteins, which can interfere with cellular function and lead to cell death.

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