Conformational diseases caused due to misfolding of proteins.

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Introduction

Proteins are the molecular motors that control our cells' most critical processes. A protein must first fold into the correct three-dimensional structure, assuming intricate tertiary and occasionally quaternary conformations, in order to accomplish its function. Although many features of protein folding are inherent to the protein's physicochemical properties, the process is complex and prone to errors. Proteins are made up of an intricate arrangement of internal folds that collapse into a final thermodynamically stable structure, and accurate folding of a protein is linked with only a minor free-energy gain compared to its numerous alternative misfolded states for many proteins. As a result, the latter may be preferred on occasion. Furthermore, many disease-causing misfolded proteins have one or more mutations that disrupt the proper fold and/or stabilise the misfolded form [1].

Misfolding of Proteins Leading to Certain Disorders

The malfunctioning of biological systems is caused by protein misfolding. Protein misfolding has been linked to a variety of disorders, which are categorised as conformational diseases.

Improper breakdown of proteins

Although cellular degradation processes like ERAD and autophagy are important for limiting the accumulation of non-functional misfolded proteins, they can also cause disease if they are overactive, destroying proteins that are defective but still have some function. As a result, incorrect protein breakdown can contribute to the progression of a more serious disease. Cystic fibrosis, which is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a plasma membrane chloride channel, is a classic example. In cystic fibrosis, the deletion of a phenylalanine residue at position 508 in the CFTR gene is the most prevalent causal mutation. The protein is misfolded as a result of this mutation, and it is then targeted for destruction.

The maturation and degradation of CFTR necessitates the involvement of numerous chaperones and co-chaperones. Mutant CFTR can evade degradation if the function of these chaperone systems is disrupted. CFTR F508 is not only more stable, but also partially functional, after knocking down AHA1, a co-chaperone that, along with HSP90, affects CFTR development. AHA1 isn't the sole chaperone-interacting protein involved in the folding of CFTR [2]. Because CHIP, an HSP70 co-chaperone, contributes in the ubiquitylation and later destruction of mutant CFTR, inhibiting CHIP function may allow more CFTR to mature and function. Inhibition of chaperone mechanisms may be therapeutically useful for people with this mutation.

Incorrect localization of proteins in cell organelles

Many proteins that localise to certain organelles must fold correctly in order to be trafficked properly, hence mutations that disrupt the right fold can result in incorrect subcellular localization. This can cause malfunction due to both the loss of function of the protein in its proper position and gain-of-function toxicity if it accumulates in the wrong place. α1-antitrypsin is a secreted protease inhibitor that causes emphysema in recessive loss-of-function cases and liver damage in dominant gain-of-function cases when it is mutated. Mutant variants of this protein are unable to fold properly and remain in the ER. Because the misfolded protein, unlike other misfolded proteins, is not destroyed, it accumulates in the ER of hepatocytes, where it is synthesised, causing liver injury [3].

Furthermore, because the altered α1-antitrypsin is not released, it cannot perform its usual cellular function of inhibiting the action of proteases in the lung, particularly neutrophil elastase. As a result, the connective tissue of the lungs is severely damaged. Although lung damage can be managed with enzyme replacement therapy.

Dominant-negative mechanism

A dominant-negative mechanism arises when a mutant protein antagonises the function of the wild-type (WT) protein, resulting in a reduction of protein activity even in a heterozygote. Mutant versions of the keratin proteins KRT5 and KRT14 cause severe blistering of the skin in epidermolysis bullosa simplex, an inherited connective tissue disorder. Keratin forms long intermediate filaments that give the epidermis of the skin its structure. Mutations in keratin linked to disease lead the protein to misfold and clump, especially in response to mechanical stress. Because a filament is made up of numerous keratin molecules, a heterozygote will produce filaments containing both wild-type and mutant keratin. The disease's dominant character is thus explained by the fact that the mutant protein present in these filaments does not function properly, putting the entire filament's function in risk [4].

Protein acquiring toxicity function

Protein conformational alterations can also result in dominant

phenotypes by inducing a protein to adopt a harmful shape. The lipid transport molecule apolipoprotein E (APOE). In 65–80 percent of people with Alzheimer's disease, at least one copy of the APOE4 allele is present (AD). The APOE4 polymorphism stabilises the protein's altered conformational fold; other alleles of this protein have an extended domain structure that is damaged by an additional salt bridge in APOE4. This interaction alters APOE4's lipid affinity, impairing mitochondrial activity and neurite out growth.

The various oncogenic proteins that drive a wide range of malignancies are a totally diverse set of proteins that acquire novel harmful activities through mutation. The first of them was found to alter the SRC (non-receptor tyrosine kinase) gene. The mutant v-SRC lacks the protein's typical self-inhibitory phosphorylation site, allowing it to promote uncontrolled cell growth. Although v-SRC is constitutively active, it is significantly less stable than the WT protein, c-SRC. The oncogenic mutation takes advantage of the fact that the HSP90 chaperone protein acts as a'reserve' or 'buffer' for protein folding. It aids in the maturation of v-SRC, as well as its localization to the membrane and avoidance of degradation. HSP90 dependence is substantially lower in wild-type SRC [5].

On-going study is revealing interesting paths for overcoming protein misfolding and so alleviating these ailments. Some of these treatments are protein-specific, while others entail modifying chaperones and degradation processes in a more general way. Because these two systems are critical for cellular protein folding in both diseased and non-pathological conditions, a greater knowledge of how they work together is critical for maximising the therapeutic benefits while limiting unfavourable side effects.

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