

Mechanisms of protein misfolding: Novel therapeutic approaches to protein-misfolding diseases - DTU Orbit (09/11/2017)

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In protein misfolding, protein molecule acquires wrong tertiary structure, thereby induces protein misfolding diseases. Protein misfolding can occur through various mechanisms. For instance, changes in environmental conditions, oxidative stress, dominant negative mutations, error in post-translational modifications, increase in degradation rate and trafficking error. All of these factors cause protein misfolding thereby leading to diseases conditions. Both in vitro and in vivo observations suggest that partially unfolded or misfolded intermediates are particularly prone to aggregation. These partially misfolded intermediates aggregate via the interaction with the complementary intermediates and consequently enhance oligomers formation that grows into fibrils and proto-fibrils. The amyloid fibrils for example, accumulate in the brain and central nervous system (CNS) as amyloid deposits in the Parkinson's disease (PD), Alzheimer's disease (AD), Prion disease and Amylo lateral Sclerosis (ALS). Furthermore, tau protein shows intrinsically disorder conformation; therefore its interaction with microtubule is impaired and this protein undergoes aggregation. This is also underlying cause of Alzheimers and other neurodegenerative diseases. Treatment of such misfolding maladies is considered as one of the most important challenges of the 21st century. Currently, several treatments strategies have been and are being discovered. These therapeutic interventions partly reversed or prevented the pathological state. More recently, a new approach was discovered, which employs nanobodies that targets multisteps in fibril formation pathway that may possibly completely cure these misfolding diseases. Keeping the above views in mind in the current review, we have comprehensively discussed the different mechanisms underlying protein misfolding thereby leading to diseases conditions and their therapeutic interventions.

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Authors: Salahuddin, P. (Ekstern), Siddiqi, M. K. (Ekstern), Khan, S. (Intern), Abdelhameed, A. S. (Ekstern), Khan, R. H. (Ekstern)

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