

Crosstalk between protein misfolding and endoplasmic reticulum stress during ageing and their role in age-related disorders

Abstract

Maintaining the proteome is crucial to retaining cell functionality and response to multiple intrinsic and extrinsic stressors. Protein misfolding increased the endoplasmic reticulum (ER) stress and activated the adaptive unfolded protein response (UPR) to restore cell homeostasis. Apoptosis occurs when ER stress is prolonged or the adaptive response fails. In healthy young cells, the ratio of protein folding machinery to quantities of misfolded proteins is balanced under normal circumstances. However, the age-related deterioration of the complex systems for handling protein misfolding is accompanied by ageing-related disruption of protein homeostasis, which results in the build-up of misfolded and aggregated proteins. This ultimately results in decreased cell viability and forms the basis of common age-related diseases called protein misfolding diseases. Proteins or protein fragments convert from their ordinarily soluble forms to insoluble fibrils or plaques in many of these disorders, which build up in various organs such as the liver, brain, or spleen. Alzheimer's, Parkinson's, type II diabetes, and cancer are diseases in this group commonly manifest in later life. Thus, protein misfolding and its prevention by chaperones and different degradation paths are becoming understood from molecular perspectives. Proteodynamics information will likely affect future interventional techniques to combat cellular stress and support healthy ageing by avoiding and treating protein conformational disorders. This review provides an overview of the diverse proteostasis machinery, protein misfolding, and ER stress involvement, which activates the UPR sensors. Here, we will discuss the crosstalk between protein misfolding and ER stress and their role in developing age-related diseases.

Keywords

Age-related diseases; Ageing; Endoplasmic reticulum stress response; Protein misfolding; Proteostasis; Unfolded protein response