Protein stress and stress proteins: implications for aging and disease

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Molecular chaperones or heat-shock proteins (Hsp-s) are a conserved guard the conformational homeostasis of proteins, and maintain signal transduction networks, regulate proliferation, differentiation, and apoptotic pathways. Upon stress, misfolded proteins liberate the heat-shock transcription factor-1 (HSF-1) from a repressing chaperone complex, and HSF-1 induces the transcription of chaperone genes. The heat-shock or stress response confers cytoprotection and assures survival during severe environmental conditions. However, there is an accumulation of protein damage, and both chaperone inducibility and chaperone function decrease and during aging. In contrast, mild heat shock, a robust heat-shock response as well as HSF-1 overexpression induces longevity, while HSF-1 knock-out markedly shortens life-span in invertebrate model organisms, suggesting that the heat-shock response limits life-span. Indeed, the robustness of the heat-shock response is the best biomarker of aging and predictor of life-span in *C. elegans*. Chaperone induction is an efficient therapeutic approach in age-related degenerative diseases involving cardiovascular diseases, cancer, diabetes, immune-problems and neurodegeneration. Both mild “hormetic” stresses (exercise, sauna, calorie restriction), trace-minerals and synthetic and plant-derived small molecules are among promising therapeutic modalities.

In my talk I will give an overview on stress, the heat-shock response and on protein homeostasis alterations during aging, and highlight some promising interventions involving the heat-shock response.