The Biology of Proteostasis: Challenges of Aging and Disease

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The health of the proteome is essential for life, which at the cellular level is orchestrated by the proteostasis network (PN) to regulate the flux of protein biogenesis from birth to death. The PN accomplishes this through the concerted activities of molecular chaperones, ubiquitin-dependent proteasomes, and autophagy pathways that are regulated primarily by the heat shock (HSR), organellar unfolded protein (UPR), and metabolic (FOXO) stress responses. Under conditions of optimal quality control as occurs during development, misfolding and aggregation are effectively suppressed even when challenged by expressed genetic polymorphisms, error-prone synthesis, and the effects of stress. However, in early adulthood the protective mechanisms for somatic tissues are blunted by signals from the germline stem cells, resulting in the collapse of proteostasis as animals attain reproductive maturity. In humans, we have also observed a decline in chaperone expression in human brain aging that is accelerated in brain tissues from patients with Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease. By testing the functionality of the chaperome in human tissue culture models for (HD) and in *C. elegans* models for AD and HD, we identified the core-sub chaperome that are essential to prevent aggregation and toxicity and declines in brain aging. These observations lead us to propose that organismal proteostasis represents the balance and coordination among multiple cell stress responses to ensure cellular and tissue health and longevity.