THE PROTEOSTASIS NETWORK IN AGE-ASSOCIATED NEURODEGENERATIVE DISEASES

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Introduction: Age-associated neurodegenerative diseases associated with protein misfolding, such as Parkinson's and Alzheimer's diseases, generate patterns of neuronal stress responses that can be better described on the level of biological networks, instead of individual genes and proteins.

Aim: Our goal is to develop a systems-based approach for the identification of novel drug targets, disease progression biomarkers, and the effect of putative therapeutics on normalizing network-level alterations.

Method: We have built a novel searchable protein-protein interaction database (Proteostasis Network Explorer) utilizing data obtained across five species from yeast to human. We integrate gene expression, proteomics, and genetics datasets into this database.

Results: Since aging is the biggest risk factor for many neurodegenerative diseases including the Alzheimer's, Parkinson's, and Huntingdon's diseases, we have overlaid gene expression datasets of brain aging onto the proteostasis network, and identified sub-networks that are regulated by aging. Furthermore, analyzing transcriptional and proteomic data from a range of human post-mortem brain tissues, we have identified both positive and negative network responses associated with stress response to neurodegeneration. These data uncover numerous similarities and differences in the proteostasis network in response to aging and age-onset diseases. For instance, we have identified an Hsp70 network, which is up-regulated in Alzheimer's disease, Parkinson's disease, and Huntington's disease. We have also found components of a mitochondrion chaperone network, including the co-chaperone Tom70, to be down-regulated in these three neurodegenerative diseases.

Conclusions: The Proteostasis Network represents novel targets for therapeutic intervention as well as potential biomarkers for disease progression and target engagement.