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Controlling Proteotoxicity with Chaparone Proteins

C. Dickey

University of South Florida, Tampa, FL 33620

The heat shock protein (Hsp) family is an evolutionarily conserved system that is charged with preventing unfolded or misfolded proteins in the cell from aggregating. In Frontal Temporal Dementias and other neurodegenerative disease intracellular aggregation of proteins such as the microtubule associated protein tau (tau) and TAR-DNA binding protein (TDP43) may result from mechanisms involving chaperone proteins like the Hsps. Due to the ability of Hsps to regulate these aberrantly accumulating proteins, therapeutic strategies are emerging that target this family of chaperones to modulate their pathobiology. For example, Hsp90 and Hsp70 each have ATPase activity that can be targeted to regulate the stability of tau and other proteins. However Hsp90 and Hsp70 are the two primary organizing scaffolds of the chaperone network and may have pleiotropic consequences for other substrates in the cell.

Therefore, our group and others have been searching for new targets in the chaperone pathway that might lead to more specific therapeutics. There are more than 150 chaperone proteins critically tied to protein quality control, and these may represent a group of potential therapeutic targets proteinopathies that have yet to be explored. New evidence suggests that specific chaperone family members can regulate the stability of tau and other aggregation-prone proteins.

Discovering the function of these chaperones could be a major step forward in drug discovery efforts for Alzheimer's disease and other neurodegenerative diseases tied to proteotoxicity.