Abstract:

Heat Shock Protein-70 (Hsp70) and its co-chaperone carboxyl-terminus of Hsp interacting protein (CHIP) are key regulators in the protein quality control (PQC) system conserved across multiple species. Together, they are essential in facilitating ubiquitin-dependent proteasomal degradation of misfolded proteins. Common neurodegenerative disorders such as Alzheimer's Disease and Parkinson's disease are hallmarked by aggregation of misfolded proteins due to a break-down of the PQC system. CHIP's multifaceted role in the PQC system suggests various implications and therapeutic targets in neurodegenerative disorders. This study aims to investigate the relationship between CHIP mutations commonly seen in neurodegenerative disorders and Hsp70 phosphorylation in the process of ubiquitin-dependent proteasomal degradation. The half-lives of CHIP mutants and the phosphorylated and unphosphorylated forms of Hsp70 were calculated as measures of protein degradation. Nano-BiT was used to quantify the level of interaction between CHIP mutants and both forms of Hsp70. Mutations in the Hsp70 binding domain of CHIP, such as G33S and the Alt Start, resulted in decrease association with HSP70. The G33S mutation significantly affected CHIP's half-life and therefore the rate of degradation of other proteins in the cells.