Engineering molecular chaperones to treat neurodegenerative diseases

Hyunju Cho

College of Medicine, Hallym University

Maintaining proper protein homeostasis is essential for healthy cells, and molecular chaperones play a crucial role in regulating it precisely. However, environmental stress, genetic mutations, and aging can diminish the overall chaperone capacity, thereby promoting protein aggregation and contributing to various protein conformational diseases such as neurodegenerative diseases. As our initial trial, we chose Huntington's disease (HD) as a target disease model and then developed a mechanistic approach to prevent mutant huntingtin (mHttex1) aggregation. We engineered the ATP-independent cytosolic chaperone PEX19, which targets peroxisomal membrane proteins to peroxisomes, to remove mHttex1 aggregates. Using a combination of random and rationalized mutagenesis approaches, we identified two human PEX19 variants (*hs*PEX19-FV and *hs*PEX19-FI). These variants effectively delay mHttex1 aggregation *in vitro* and in cellular HD models. The mutated hydrophobic residue in the α4 helix of *hs*PEX19 variants binds to the N17 domain of mHttex1, thereby inhibiting the initial aggregation process. Overexpression of the *hs*PEX19-FV variant rescues HD-associated phenotypes in primary striatal neurons and in *Drosophila*. Therefore, our study suggests that fine-tuning the sequences of ATP-independent membrane protein chaperones could be a feasible approach to designing therapeutic chaperones for HD and potentially other diseases linked to protein aggregation.