ABSTRACT

Targeted protein degradation shows promising results as an effective therapeutic strategy to target the undruggable pathological proteins by using cell's own quality control. The enhancement of ubiquitin proteasome system is one of the ways to regulate the proteostasis by clearance of misfolded intracellular proteins implicated in the neurodegenerative diseases. There is a need to replace the small molecules with the peptides as a ligand for E3 ligase in the design of a heterobifunctional degrader molecule to overcome the limitations of off-target effects, preserving the domains of functional proteins and compatible for oral administration. Our study hypothesized that the peptide fragment derived from C-terminal of Amyloid Precursor Protein (APP) would bind to one of the target E3 ligases that is ubiquitously expressed in the human neuroblastoma SH-SY5Y cells. Our experimental study concluded that the APP derived peptide fragment binds to Kelch repeat and BTB domain-containing protein (KBTB4_Human) E3 ligase in the SH-SY5Y cells. In motor neuron diseases such as ALS and FTD, the pathological form of TDP43 protein being one of the undruggable targets, we also expressed and purified the protein using bacterial system.

Keywords: Proteostasis, Ubiquitin Proteasome system, E3 ligase, Amyloid Precursor Protein, TDP43, Heterobifunctional degrader