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De Novo Rational Design of Peptide-Based Protein–Protein Inhibitors (Pep-PPIs) Approach by Mapping the Interaction Motifs of the PP Interface and Physicochemical Filtration: A Case on p25-Cdk5-Mediated Neurodegenerative Diseases

Protein–protein interactions, or PPIs, are a part of every biological activity and have been linked to a number of diseases, including cancer, infectious diseases, and neurological disorders. As such, targeting PPIs is considered a strategic and vital approach in the development of new medications. Nonetheless, the wide and flat contact interface makes it difficult to find small-molecule PP inhibitors. An alternative strategy would be to use the PPI interaction motifs as building blocks for the design of peptide-based inhibitors. Herein, we designed 12-mer peptide inhibitors to target p25-inducing-cyclin-dependent kinase (Cdk5) hyperregulation, a PPI that has been shown to perpetuate neuroinflammation, which is one of the major causal implications of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and frontotemporal dementia. We generated a library of 5 062 500 peptide combination sequences (PCS) derived from the interaction motif of Cdk5/p25 PP interface. The 20 amino acids were differentiated into six groups, namely, hydrophobic (aliphatic), aromatic, basic, acidic, unique, and polar uncharged, on the basis of their physiochemical properties. To preserve the interaction motif necessary for ideal binding, de novo modeling of all possible peptide sequence substitutions was considered. A set of filters, backed by the Support Vector Machine (SVM) algorithm, was then used to create a shortlisted custom peptide library that met specific bioavailability, toxicity, and therapeutic relevance, leading to a refined library of 15 PCS. A greedy algorithm and coarse-grained force field were used to predict peptide structure and folding before subsequent modeling studies. Molecular docking was performed to estimate the relative binding affinities, and out of the top hits, Pep15 was subjected to molecular dynamics simulations and binding free-energy calculations in comparison to a known peptide inhibitor with experimental data (template peptide). Interestingly, the identified peptide through our protocol, Pep15, was found to show a significantly higher binding affinity than the reference template peptide (-48.10 ± 0.23 kcal/mol and -17.53 ± 0.27 kcal/mol, respectively). In comparison to the template peptide, Pep15 was found to possess a more compact and buried surface area, tighter binding landscape, and reduced conformational variability, leading to enhanced structural and kinetic stability of the Cdk5/p25 complex. Notably, both peptide inhibitors were found to have a minimal impact on the architectural integrity of the Cdk5/p25 secondary structure.

Herein, we propose Pep15 as a novel and potentially disruptive peptide drug for Cdk5/p25-mediated neurodegenerative phenotypes that require further clinical investigation. The systematic protocol and findings of this report would serve as a valuable tool in the identification of critical PPI interface reactive residues, designing of analogs, and identification of more potent peptide-based PPI inhibitors.

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