Rational Design of Amyloid Aggregation Inhibitors

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The molecular basis of amyloid aggregation is still unclear and the exact causative agent of Alzheimer's disease (AD) is yet to be understood. The majority of AD therapies aim to alleviate symptoms by increasing the availability of neurotransmitters in the brain. In this talk, I will briefly overview the field and introduce our recent work on the structure-based rational design of amyloid-β (1-42) point mutants that suppress amyloid aggregation and alleviate cytotoxicity. Through multi-step computational analyses on the atom-level structure of fibrils, we designed mutant constructs to inhibit the fibrillation process. Using a multidisciplinary biophysical approach, we investigated the physicochemical properties and unveiled the structural basis for decreased self-assembly. We confirmed by cell-based assays that the proposed mutant candidates showed reduced cytotoxicity.