ATOMIC SCALE SIMULATION OF AMYLOID BETA WITH DISMANTLING PEPTIDE-BASED INHIBITORS

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EXECUTIVE SUMMARY

Aggregation of amyloid beta (AB) proteins plays a fundamental role in Alzheimer's disease. Several inhibitors of AB aggregation have been proposed in the literature, but no effective treatment is yet available. In this work, the research team introduced novel multivalent polymer–peptide conjugates (mPPCs) that can disaggregate or inhibit AB formation. Moreover, the team recently evaluated new macrocyclic peptidomimetic (MP) libraries that can also hinder AB aggregation.

The researchers used all-atom molecular dynamics (MD) simulations to investigate how mPPCs and MPs bind AB fibrils and alter their stability. Simulations of mPPCs alone or in the presence of AB show that mPPCs self-aggregate in solution, but in the presence of AB they strongly interact with AB through both their peptide and backbone moieties. Furthermore, a docking analysis based on the simulation results reveals that inhibitors may destabilize AB through introducing defects in the fibril.

RESEARCH CHALLENGE

Protein aggregation is implicated in major pathophysiological conditions including Alzheimer's and Parkinson's disease [1]. The occurrence of Alzheimer's disease, in particular, has been linked to the formation of toxic aggregates of amyloid beta (AB) peptides. Although several inhibitors have been developed, the aggregation mechanism is still poorly understood. The research team has recently developed a novel class of hydrophilic, high molecular weight polymers, mPPCs, that bear multiple copies of peptides and can inhibit AB fibril formation (Fig. 1) [2,3]. This multivalency strategy uses multiple simultaneous interactions of the ligand with AB to enhance the affinity. Another strategy involves the use of MP that are stable under physiological conditions and favor interactions with AB owing to their preorganized structure. However, little is known about how these molecular architectures interact with the target protein and what can be done to enhance their effect and increase their specificity.

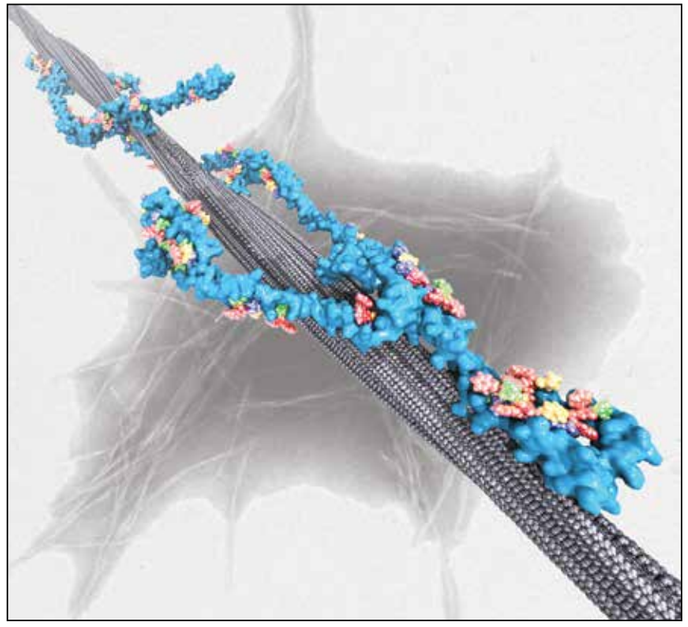

Figure 1: Molecular model of a putative inhibitory mechanism of a polymer inhibitor (backbone in cyan and active peptides in multicolor) wrapping around an amyloid beta fibril. The image in the background illustrates fibril aggregates forming an amyloid beta plaque.

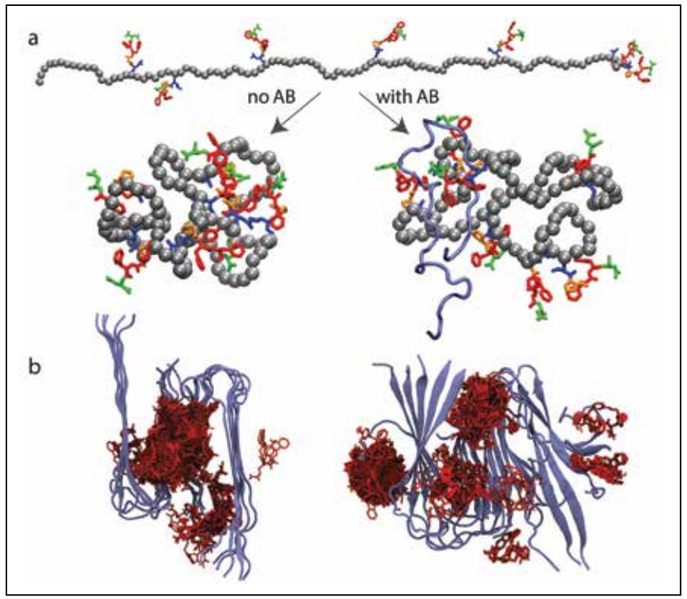

Figure 2: (a) A representative inhibitor polymer composed of 100 monomers (black beads) and multiple peptides (multicolor). In the absence of amyloid beta, the polymer forms a pseudospherical aggregate. With amyloid beta (purple strand), the polymer wraps around the proteic strain. (b) Docking poses (red) of a macrocyclic peptidomimetic for two different conformations of an amyloid beta oligomer.

METHODS & CODES

All MD simulations were performed using NAMD [4], a GPU-accelerated code that has been optimized to run on Blue Waters. In-house scripts using VMD generated mPPC models with different compositions, molecular weights, and peptide loadings [5]. The latter software can also be used to remotely visualize trajectories on Blue Waters. The AB oligomer was obtained from the Protein Data Bank (code: 2LMN).

RESULTS & IMPACT

The simulations of mPPC polymers in solution highlighted that all polymers form pseudospherical self-aggregates within a few hundreds of nanoseconds (Fig. 2a). This self-aggregation resulted from hydrophobic and hydrogen bond interactions among components of the polymers. In particular, the size of mPPC aggregates did not increase monotonously with the peptide loading but rather decreased at high values. The size contraction of mPPCs was ascribed to the increase of hydrophobic contacts as the number of peptides grafted onto the polymer increased, causing a more tightly packed aggregate. Interestingly, in the presence of AB, mPPCs wrap around the protein and form a stable complex. From the analysis of contacts and hydrogen bonds, the research team concluded that stabilization of this complex was significantly enhanced by the mPPC-backbone interaction with AB, confirming the effectiveness of the multivalent design of the polymers. These analyses also revealed that proline residues of mPPCs contribute the most to interactions with AB.

MD simulations performed on an AB oligomer provided multiple conformations of the protein. Molecular docking of an MP performed on these conformations (Fig. 2b) showed that the inhibitors can intercalate inside defects generated owing to thermal fluctuations, as captured during the simulation, in the AB secondary structure. Perturbed beta-sheet structures of AB can allow the insertion of inhibitors, which in turn will weaken and eventually dismantle the fibril structure.

Overall, the insights obtained from these simulations provide a molecular-level mechanism associated with the inhibition of AB aggregation and will support the design of new inhibitors.

WHY BLUE WATERS

The resources provided by Blue Waters in terms of computational power and network performance were essential to carrying out this project because of the need for simulation of a large data set. The large computer allocation allowed for the simulation of multiple systems, some of which were replicated multiple times with varying initial conditions to enhance sampling.

PUBLICATIONS & DATA SETS

X. Jiang *et al.*, "Multivalent polymer–peptide conjugates—a general paradigm for inhibiting amyloid beta peptide aggregation," in preparation, 2019.

X. Jiang *et al.*, "Amyloid beta peptide aggregation inhibitors from a macrocyclic peptidomemics library," in preparation, 2019.