National Institute of Technology Rourkela

Synopsis Seminar

Seminar Title	: Rationally Designed Peptides as Inhibitors of Hen Egg-White Lysozyme Amyloid Formation
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Venue	: Seminar Room, BM Dept.
Date and Time	: 05 Jul 2024 (4.00 pm)

Abstract : Misfolded and natively disordered globular proteins have a tendency to aggregate together to form fibrous, proteinaceous deposits referred to as amyloid fibrils. Formation and deposition of such insoluble fibrils are the hallmarks of a broad group of diseases known as amyloidosis, such as Amyloid-Beta (A&beta) in Alzheimer&rsquos disease (AD), human Islet Amyloid Polypeptide (hIAPP, amylin) in type 2 diabetes, &alpha-synuclein (&alpha-syn) in Parkinson&rsquos disease (PD) and so on. The fact that these proteins do not share any significant sequence or structural homology in their native states makes therapy quite challenging. Hotspot regions, known as aggregation-prone regions (APR), within the sequence of the amyloidogenic protein/peptides, are the nucleation point upon which fibril progression takes place. In the research presented in this thesis, we have meticulously designed synthetic hexapeptides based on the APR sequence of hen egg-white lysozyme (HEWL, a model amyloidogenic protein) and explored their anti-amyloidogenic potency on *in-vitro* amyloid formation of HEWL at acidic pH and physiological pH, and the peptide inhibitors are referred to as SqPs (Sequence-based Peptides). Notably, SqP1, amongst the others, exhibited a remarkable lysozyme amyloid inhibition rate of over 70% and ~50% at pH 2.2 and pH 7.5. Further, SqP1 was modified by incorporating either acidic (Aspartate or Glutamate) or basic (Lysine or Arginine) amino acid residues to impart net charge to the peptide. Out of these, Asp-modified SqP1 (SqP4) and Arg-modified SqP1 (SqP7) were further chosen based on computational docking, and the anti-amyloidogenic propensity of these modified peptides was further investigated. Interestingly, as the conditions chosen for conducting this study are different (acidic and neutral), SqP4 displayed a protonation-state-dependent anti-amyloidogenic propensity against HEWL amyloid formation. This study enabled us to shed light on the factors kept in mind while designing a sequence-based anti-amyloidogenic peptide inhibitor the incorporation of amino acid residues should not only be done to achieve favorable interactions but also to carefully avoid any unfavorable interactions leading to non-specific binding. Furthermore, the Arg-modified SqP1 (SqP7) showed excellent amyloid inhibition capability at both pH conditions and was further chosen as a coating agent on gold nanoparticles. The anti-amyloidogenic capability of the synthesized peptide-coated gold nanoparticles (SqP7-AuNP) was further evaluated, and it was observed that upon coating, the efficacy of SqP7 was increased around 10 times molarity-wise. The findings of this work were achieved using molecular docking techniques alongside an array of biophysical methodologies, including fluorescence spectroscopy, UV-vis spectroscopy, FTIR spectroscopy, CD spectral analysis, confocal laser microscopy, and transmission electron microscopy. The insights gained from this study can be further utilized to increase the efficacy of anti-amyloidogenic synthetic peptide inhibitors and aid in the development of synthetic peptides as therapeutics against other amyloid-related diseases such as Parkinson&rsquos disease, Alzheimer&rsquos disease, type II diabetes, etc. Moreover, the findings from this work can overall increase the quality of fundamental research and ventures taken in the future in the field of amyloid-related diseases.

Keywords: Amyloid Inhibition inhibitory peptides, HEWL protein, Amyloidogenic-prone region (APR), surface functionalization, gold nanoparticles and Inhibition of amyloids.