CHAPTER 12

SUMMARY AND FUTURE PROSPECTS

Summary and Future prospects

12.1. Overview of results:

The main theme of the current thesis involves structural characterization of the probable initial seed structure of $A\beta_{1-42}$ peptide responsible for aggregation. Furthermore, the self-assembly mechanism of $A\beta_{1-42}$ peptide, and the cross-seeding interaction of $A\beta_{1-42}$ peptide with Tau protein was investigated. Apart from that we have used disorder predictors to find out the probable disordered regions of the $A\beta_{1-42}$ peptide. We have also identified different interactions that help in stabilizing the $A\beta_{1-42}$ peptide oligomers and polymorphs of $A\beta_{1-42}$ fibril. Finally, we have also devised three different methods to inhibit the aggregation of $A\beta_{1-42}$ peptide in early and later stage.

In the first part of the thesis, we predicted the structural features of the probable initial seed structure of $A\beta_{1-42}$ peptide responsible for aggregation using unrestrained folding simulation. We found the seed structure to be highly rich in β-strands at the C-terminal end.

In the second part of the thesis, the dimerization mechanism of $A\beta_{17-42}$ peptide was examined. With the aim to find out the interactions that plays an important role in stabilizing the dimers, we examined their interaction profile. Monomeric units of $A\beta_{17-42}$ peptide dimer were found to have an increased β-strands propensity at the hydrophobic regions encompassing the CHC region and the simulation studies showed this hydrophobic region encompassing the CHC region to be crucial in dimerization. The cross-sequence interaction studies of $A\beta_{25-35}$ peptide and $Tau_{273-284}$ revealed $A\beta_{1-42}$ peptide to have a high affinity to form dimer complex with Tau which consequently advances to form aggregates. Moreover, analyses results of the $A\beta_{1-42}$ peptide with disorder predictors are also in good agreement with our results obtained from the unrestrained folding simulation.

We also found formation of a stable $A\beta_{1-42}$ peptide oligomer to occur through secondary structural transitions from α-helix to random coils which may further form β-strands. From the interaction study, we found inter-peptide salt bridges, hydrogen bonds and non-bonded contacts to play a crucial role in stabilizing the oligomers. We also carried out interaction studies on the polymorphs of $A\beta_{1-42}$ fibril which have been reported to be present in the senile plaques. The results show that hydrophobic residues in the CHC region and C-terminal region play a vital role in the formation of the

aggregates. Furthermore, specific hydrophobic residues were found to play a vital role in the formation of the aggregates.

In the last part of the thesis, we demonstrated different methods to inhibit the aggregation of $A\beta_{1-42}$ peptide in the early and later stage. At first, we showed ss-oligonucleotide as a potent inhibitor which helps in retaining the native α-helical structure of $A\beta_{1-42}$ peptide thus preventing the formation of dimers further downstream. We also demonstrated that the ss-oligonucleotide facilitates the disassembly of $A\beta_{17-42}$ peptide dimer. We found electrostatic interactions, hydrogen bonds and hydrophobic interactions between the $A\beta_{17-42}$ peptide dimer and the ss-oligonucleotide to play an important role in disassembling the dimer.

In our second approach, we demonstrated the inhibitory effect of $A\beta_{1-40}$ peptide on the aggregation propensity of $A\beta_{1-42}$ peptide. Our findings proved that in the presence of the $A\beta_{1-40}$ peptide, specific regions important for fibril formation of $A\beta_{1-42}$ peptide exhibited a high fluctuation as well as the distance between the residues involved in salt bridge formation increased. From the protein-protein interaction study, we found the N-terminal regions of $A\beta_{1-42}$ peptide to be involved in forming the hetero-dimer complex with $A\beta_{1-40}$ peptide.

Moreover, we used 6 mer-peptide (IGLMVV) as an inhibitor of $A\beta_{1-42}$ peptide aggregation. The MD simulation of the peptide and fibril complex showed that the peptide binds to the fibril with a high affinity and thus imparts it inhibitory effect by dissociating the fibril to single strands. Our findings exclusively with $A\beta_{1-42}$ monomer revealed that the 6-mer peptide affected the secondary structural changes in the monomer by decreasing the β-strand contents.

12.2. Future prospects:

Time and again, good research leads to more questions than answers. This thesis gave an atomistic insight about aggregation-prone $A\beta_{1-42}$ peptide, different interactions involved in the initial stages of aggregation and finally some approaches to overcome the aggregation. This work has further possibilities that include:

i. The identification of the molecular and metabolic regulators of $A\beta_{1-42}$ peptide signaling pathways that regulate $A\beta_{1-42}$ peptide production and its toxicity will pave way for the development of the therapeutic targets which can inhibit the disease progression and also reduce the toxicity level.

ii. Study on the apparent increased vulnerability of hippocampal, temporal and parietal neurons to the pathology of AD will be very helpful. Answers to this question may facilitate the development of sensitive assays of dysfunction in these neural circuits, which can be used as the theragnostics markers.

iii. Need for validation of inhibitory effect of potential analogue of the 6-mer peptide.