Conformational ensembles of $A\beta_{1-42}$ dimer and its Dutch E22Q mutant in Alzheimer disease

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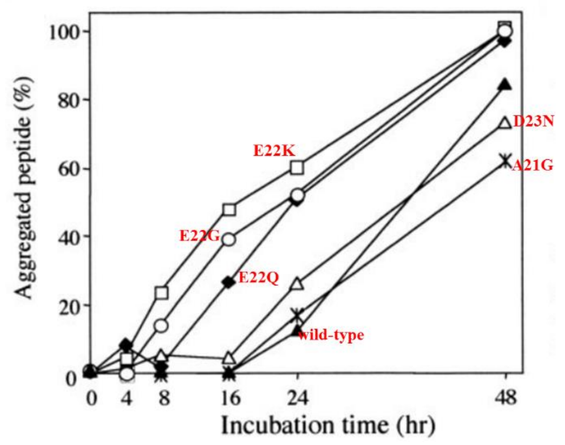
Introduction

Alzheimer's disease is associated with the aggregation of amyloid-β (Aβ) peptides into toxic prefibrillar aggregates[1,2]. Previous studies reported that the $A\beta_{1-42}$ dimer was the smallest toxic species in Alzheimer's disease[3] and the dutch E22Q mutant was much more toxic than $A\beta_{1-42}$[4]. Inverstigating the dimeric structures of $A\beta_{1-42}$ and its E22Q mutant is crucial for understanding their different cytotoxicity. However, due to the transient nature of oligomers, the atomic-level structures of $A\beta_{1-42}$ dimer and its E22Q mutant are largely unknown.

Neurotoxicity in PC12 cells of Aβ derivatives estimated by the MTT assay

Aβ derivatives	IC_{50}
	μM ± S.D.
Aβ40 (Wild-type)	>100
A21G-Aβ40 (Flemish)	>100
E22Q-Aβ40 (Dutch)	3.4 ± 0.91
E22K-Aβ40 (Italian)	11 ± 2.2
E22G-Aβ40 (Arctic)	11 ± 2.2
D23N-Aβ40 (Iowa)	78
E22P-Aβ40	8.0 ± 0.72
Aβ42 (Wild-type)	0.97 ± 0.18
A21G-Aβ42 (Flemish)	1.7 ± 0.30
E22Q-Aβ42 (Dutch)	0.068 ± 0.01
E22K-Aβ42 (Italian)	0.14 ± 0.030
E22G-Aβ42 (Arctic)	0.14 ± 0.050
D23N-Aβ42 (Iowa)	0.38 ± 0.16
E22P-Aβ42	0.084 ± 0.011
E22V-Aβ42	>100

Aβ42 E22Q mutant shows most serious neurotoxic effect[4]



Aβ42 E22Q mutant shows strong aggregation effect[4]

Materials and Methods

Systems: $A\beta_{1-42}$ dimer: 1IYT (PDB:ID)
$A\beta_{1-42}$ E22Q dimer: 1IYT only with E22Q mutation

Amino Acid Sequence of $A\beta_{1-42}$ **:**
NH_3^+-DAEFRHDSGY[10]EVHHQKLVFF[20]AEDVGSNKGA[30]IIGLMVGGVV[40]IA-COO^-

Simulation Method: REMD in NPT ensemble, P: 1 bar
Temperature: 308.5-406.2 K, Box size: 7.0*7.0*7.0 nm

Force Field: Amber99sb-ILDN

Water Model: TIP3P

Software Packages: Gromacs-4.5.3 and VMD

Results

1. Convergence check for $A\beta_{1-42}$ dimer and E22Q dimer.

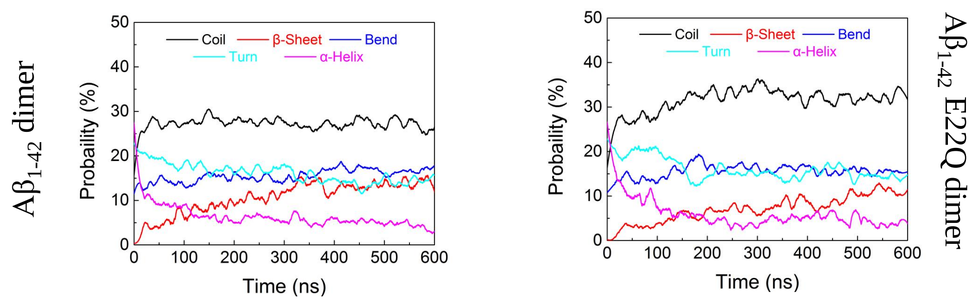


Figure 1. Time evolution of secondary structure.

2. The average secondary structure propensity and residue-based β-sheet propensity are different between $A\beta_{1-42}$ dimer and E22Q dimer.

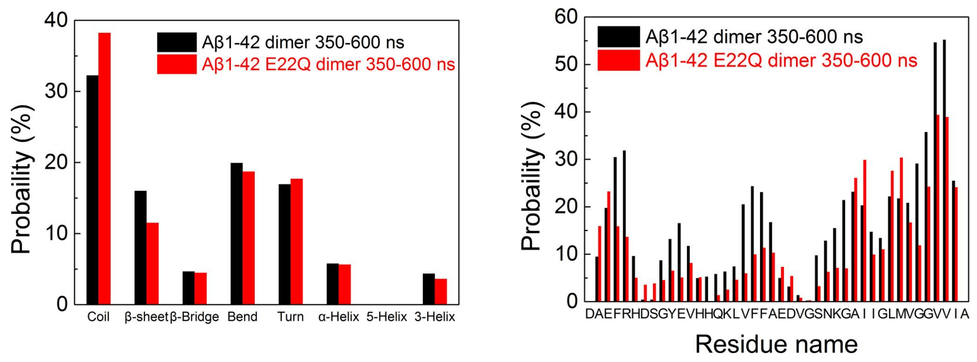


Figure 2. Average secondary structure propensity and β-sheet probability of each residue of $A\beta_{1-42}$ dimer and E22Q.

3. Free energy landscape of $A\beta_{1-42}$ dimer and its E22Q mutant.

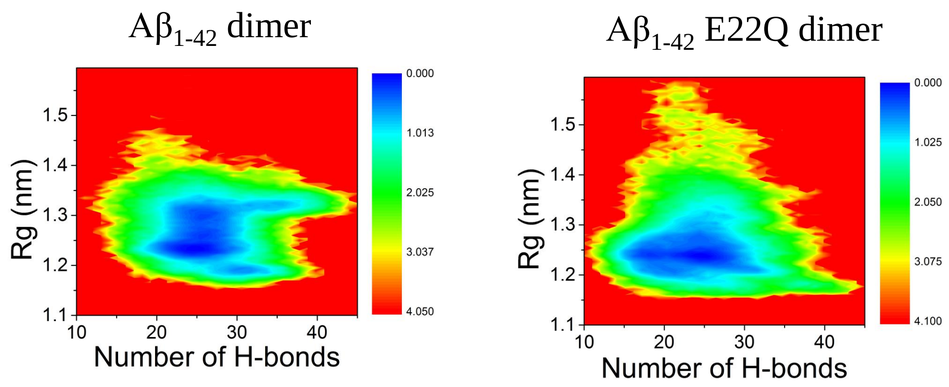
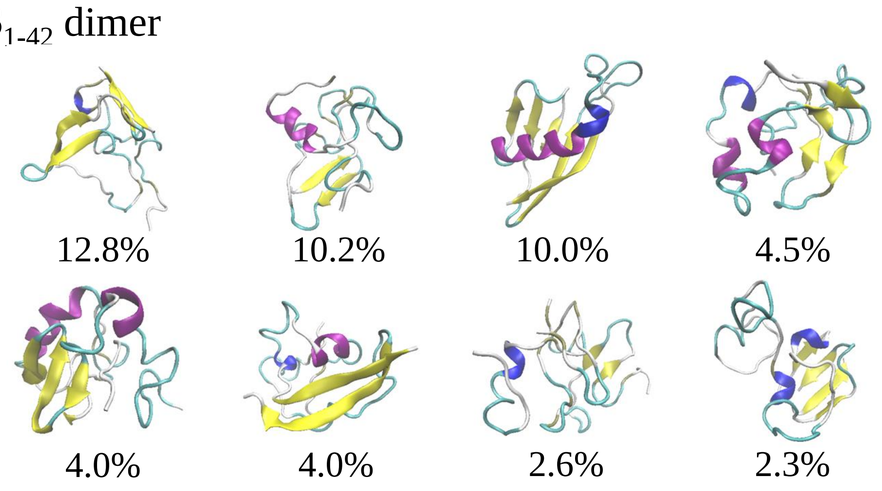


Figure 3. Free energy surfaces (in kcal/mol) as a function of the total number of H-bonds and the radius of gyration of the dimer.

4. Clusters are different between $A\beta_{1-42}$ dimer and its E22Q mutant.

(A) $A\beta_{1-42}$ dimer



(B) $A\beta_{1-42}$ E22Q dimer

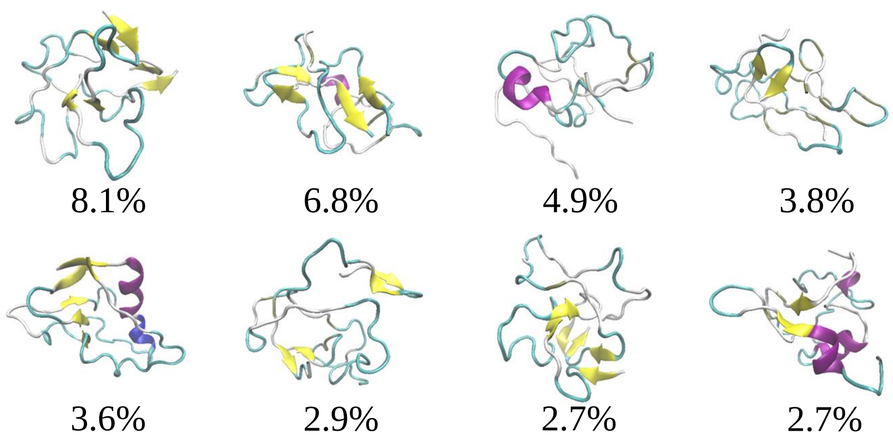


Figure 4. Representative conformations of the top eight most-populated clusters for (A) $A\beta_{1-42}$ dimer and (B) E22Q mutant dimer.

Conclusions

We find that the average β-sheet probability for $A\beta_{1-42}$ dimer is 16%, while it is only 8% for its E22Q mutant. The $A\beta_{1-42}$ dimer has a preference to form long β-sheet, but its E22Q mutant preferentially forms short β-sheet. This study provides insights into the equilibrium structure of the $A\beta_{1-42}$ dimer and its E22Q mutant in aqueous solution, opening a new avenue for a comprehensive understanding of the impact of pathogenic and protective mutations in early-stage Alzheimer's disease on a molecular level.

References

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4. Murakami K, Irie K, et al. *J. Biol. Chem.*, 278(46): 46179-46187(2003).