Characterizing Effect of Glutamine Position on A-Beta Fiber Structure, Year II

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Amyloids are misfolded proteins that have been correlated with numerous human neurodegenerative diseases including Alzheimer's disease, but the nature of the misfolded structure that leads to disease is not known. Amyloid Beta (Aß) peptide, the primary component of amyloid plaques in the brains of Alzheimer's patients, was targeted for the study. This study focuses on the nucleating core of Aß Dutch mutant, Ac-16KLVFFA22Q-NH2 or E22Q. E22Q has been known to assemble into fibers with parallel strand orientation due to interstrand hydrogen bonds between glutamines (Q). Studies of several mutants of E22Q, including L17Q (KQVFFAE), V18Q (KLQFFAE), and A21Q (KLVFFQE), showed that the position of Q affects tertiary and quaternary structures. This study focused on the effect Q would have when placed at the peptide's nucleating core. Two mutants, F19Q (KLVQFAE) and F20Q (KLVFQAE) were synthesized. Isotope-edited infrared spectroscopy (IE-IR), which probes molecular vibrations at specific residues, was used to study the structure and dynamics of the assembly. Transmission electron microscopy (TEM) was optimized to visualize the overall morphology of the amyloids. Despite their identical composition and close proximity with regard to Q position, their molecular structure and assembly kinetics are drastically different. These findings give further insight into not only glutamine's positional effect but also the importance of double phenylalanine interactions in Aß assembly.

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