

KINETICS OF AMYLOID FIBRIL FORMATION

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Prolonged exposure of proteins with reactive oxygen species (ROS) contributes to processes that induce irreversible structural damage and alter protein activity. The amyloidoses are a group of protein misfolding diseases including Alzheimer's disease (AD) that occur from deposition of protein fibrils in organs and tissues [1]. We are investigating the effects of amino acid side chain oxidation in amyloid assemblies by applying radical probe mass spectrometry (RP-MS) approaches [2, 3]. Transthyretin (TTR) is a homotetrameric plasma protein and several of its variants are prone to fibril formation [4]. The wild type (WT) and a V30M TTR mutant were reacted with reactive oxygen species (ROS) over extended reaction timescales from several minutes to hours. The extent and sites of amino acid side chain oxidation were determined by mass spectrometry analysis. Kinetics of fibril formation of the native and oxidized proteins were then compared by turbidity assays.

Oxidation had a dramatic affect on initial rates of fibril growth for both proteins. In the case of WT TTR, oxidation inhibited the fibril growth by approximately 76% and for the V30M TTR by nearly 90%. Oxidation affected the kinetics of fibril formation for V30M TTR more than the WT TTR consistent with the fact the V30M TTR contains one more methionine residue available for oxidation. The inhibition effects of fibril formation for these oxidized proteins are intriguing and demonstrate that side chain oxidation can be used a method of inducing mutations in protein sequences to investigate amino acids that are critical in preserving a protein's structure and stability [3].

References:

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