Controlled and Selective Photo-oxidation of Amyloid-β Fibrils by Oligomeric p-Phenylene Ethynylenes

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Alzheimer's disease is an incurable disorder believed to be caused by amyloid protein misfolding and aggregation. Among the therapeutic targets that have been evaluated, disassembly and clearance of amyloid aggregates remain an attractive approach. Photodynamic therapy (PDT), which has been mainly investigated in oncology, may be used to trigger the clearance of amyloid aggregates through their oxidation. In PDT, a photosensitizer is used to generate reactive oxygen species upon light exposure. However, off-target oxidation is problematic as the photosensitizer activity is always turned-on under photoradiation. We have recently shown that oligomeric *p*-phenylene ethynylenes (OPEs) selectively bind to the aggregate conformation of amyloid proteins such as amyloid-β (Aβ40) and display fluorescence turn-on upon binding. Additionally, OPE photosensitization was found to be activated with fluorescence turn-on. In this study, we are evaluating the capability of OPEs to selectively photo-oxidize Aβ40 fibrils upon binding and compare it to a well-known photosensitizer Methylene Blue. The selective oxidation of fibrils over monomers are investigated by a combination of characterization methods including DNPH dot blot, mass spectrometry, and amino acid analysis. The effects of oxidation on amyloid fibril morphology and secondary structures are monitored by TEM imaging and circular dichroism spectroscopy. The effect of oxidation on amyloid fibril toxicity is additionally evaluated. Our results show that an anionic OPE selectively sensitized the oxidation of Aβ40 fibrils, but not monomers. The likely oxidization sites are Histidine 13, Histidine 14 and Methionine 35. The oxidation of Aβ40 fibrils also led to their disassembly into shorter aggregates characterized by low cell toxicity. Our findings demonstrate that OPEs can selectively oxidize amyloid fibrils with minimal off-target oxidation. This investigation contributes to a better understanding of the controllable photosensitizer activity of OPEs and could lead to the development of a new therapeutic approach for amyloid proteinopathies.