Shedding light on neurodegeneration: small angle X-ray scattering and misfolded proteins

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The misfolding pathways that lead to cytotoxic species vary between diseases such as Alzheimer's (AD), Huntington's and Parkinson's but there is a common link in that they all involve some form of oligomeric species, in contrast to the extra- or intra-cellular fibrillar deposits of aggregated protein that are regarded as end products of the pathological process (Villemagne *et al.*, 2010). To elucidate possible folding pathways for the amyloid β peptide of AD (Aβ) we made time-resolved, stopped-flow SAXS measurements at the Australian Synchrotron on Aβ 1-40 and Aβ 1-42 peptides in dilute NaOH (13mM) that were rapidly mixed with pH 6.9 phosphate buffered saline containing Cu^{2+} ions. These showed that protofibril formation occurred in less than one second in either control or Cu^{2+}–containing buffer and that evolution of the fibrils in subsequent seconds followed a non-linear pattern. Static measurements on the peptides that had been reacted with sub-micellar concentrations of the lipid mimetic, N-lauroylaminopropyl-N′,N′- dimethylamine oxide (LDAO) and a dipeptide formed of tyrosine 10 cross-linked Aβ 1-40 (Kok *et al.*, 2009), however, gave a stable well-defined "Y" shaped structure for both the di-tyrosine linked peptide and LDAO- associated Aβ 1-42. The "Y" shape is reminiscent of the Fc antibody fragment. Since the di-tyrosine linked peptide is neurotoxic, as in the case of cytotoxic antibodies, its two arms may carry ligands able to cross-link cell membrane receptors to initiate a cytotoxic cascade.

Villemagne VL, Perez KA, Pike KE, Kok WM, Rowe CC, White AR, Bourgeat P, Salvado O, Bedo J, Hutton CA, Faux NG, Masters CL, Barnham KJ (2010) *Journal of Neuroscience* **30**: 6315-22.

Kok WM, Scanlon DB, Karas JA, Miles LA, Tew DJ, Parker MW, Barnham KJ,Hutton CA (2009) *Chemical Communications (Cambridge, England)* **7**: 6228-30.