AB NEUROTOXICITY IS MEDIATED BY ONGOING NUCLEATED POLYMERIZATION PROCESS RATHER THAN BY DISCRETE AB SPECIES

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Introduction: The identification of toxic Aβ species and/or the process of their formation is crucial for understanding the mechanism(s) of Aβ neurotoxicity in Alzheimer's disease (AD), and also to development of effective diagnostic and therapeutic interventions.

Aims: To elucidate the structural basis of Aβ toxicity and identify the toxic oligomer species.

Methods: Size exclusion chromatography, cell culture, cytotoxicity assays, electron microscopy and thioflavin binding.

Results: We observed that crude Aβ42 preparations, containing monomeric and heterogeneous mixture of Aβ42 oligomers, were more toxic than purified monomeric, protofibrillar fractions or fibrils. The toxicity of protofibrils was directly linked to their interactions with monomeric Aβ42 and strongly dependent on their ability to convert into amyloid fibrils. Subfractionation of protofibrils diminished their fibrillization and toxicity, whereas reintroduction of monomeric Aβ42 into purified protofibril fractions restored amyloid formation and enhanced their toxicity. Selective removal of monomeric Aβ42 from these preparations, using insulin degrading enzyme, reversed the toxicity of Aβ42 protofibrils.

Conclusions: Together, our findings demonstrate that Aβ42 toxicity is not linked to specific prefibrillar aggregate(s), but rather to the ability of these species to grow and undergo fibril formation, which depends on the presence of monomeric Aβ42. These findings contribute significantly to the understanding of amyloid formation and toxicity in AD, provide novel insight into mechanisms of Aβ protofibrils toxicity and carry important implications for designing anti-amyloid therapies.