Understanding Amyloid Oligomers and Finding Opportunities toward Combating Neurodegenerative Diseases: Stories of Amyloid-β and TDP-43

Yun-Ru (Ruby) Chen1

陳韻如

*1The Genomics Research Center, Academia Sinica, Taipei, Taiwan*

Correspondence e-mail address: [yrchen@gate.sinica.edu.tw](mailto:yrchen@gate.sinica.edu.tw)

Amyloids comprising amyloid fibrils are the pathogenic hallmarks of many neurodegenerative diseases including the most prevalent Alzheimer’s disease (AD) in the elderly. Amyloid formation is initiated by protein misfolding followed by self-association to ultimately form amyloid fibrils with cross-β spines. The discovery of toxic pre-fibrillar oligomers underscores the importance of understanding the formation of amyloid oligomers and its role in fibrillization. Here, I will first discuss with you our research focuses on folding and misfolding of amyloid-β (Aβ) in AD. We have examined the folding and misfolding properties of Aβ40 and Aβ42 isoforms, the familial Aβ mutants, and influence of metal ions. Secondly, TDP-43 proteinopathies, consisting of several neurodegenerative diseases including frontotemporal lobar dementia (FTLD), amyotrophic lateral sclerosis (ALS), and AD, are characterized by inclusion bodies formed by polyubiquitinated and hyperphosphorylated full-length and truncated TDP-43. The structural properties of TDP-43 aggregates and their relationship to the pathogenesis are still ambiguous. We demonstrated that the recombinant full-length human TDP-43 forms toxic, spherical oligomers that share common properties with amyloid oligomers. TDP-43 oligomers are capable of cross-seeding Alzheimer’s amyloid-β to form amyloid oligomers, showing the inter-convertability between the amyloid species. By developing a conformational TDP-43 oligomer antibody, we demonstrated that such oligomers are present in the forebrain of transgenic TDP-43 mice and FTLD-TDP patients. Further studies showed TDP-43 oligomers are also present in ALS patients. Our results suggest aside from filamentous aggregates TDP-43 oligomers may play a role in TDP-43 pathogenesis including AD.

References:

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